

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

PYRIDINE

(CAS NO. 110-86-1)

IN F344/N RATS, WISTAR RATS, AND B6C3F₁ MICE

(DRINKING WATER STUDIES)

Scheduled Peer Review Date: 9-10 December 1997

NOTICE

This is a DRAFT Technical Report prepared for public review and comment. Until this DRAFT has been reviewed and approved by the NTP Board of Scientific Counselors' Technical Reports Review Subcommittee in public session, the interpretations described herein do not represent the official scientific position of the National Toxicology Program. Following peer review, readers should contact the NTP for the final version of this Technical Report.

NTP TR 470

NIH Publication No. 98-3960

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NOTE TO THE READER

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are also available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: <http://ntp-server.niehs.nih.gov>.

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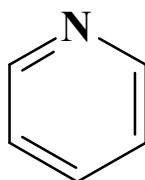
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CONTENTS

ABSTRACT		7
EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY		16
TECHNICAL REPORTS REVIEW SUBCOMMITTEE		17
SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS		18
INTRODUCTION		19
MATERIALS AND METHODS		33
RESULTS		49
DISCUSSION AND CONCLUSIONS		93
REFERENCES		103
APPENDIX A	Summary of Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine	A-1
APPENDIX B	Summary of Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine	B-1
APPENDIX C	Summary of Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine	C-1
APPENDIX D	Summary of Lesions in Male Mice in the 2-Year Drinking Water Study of Pyridine	D-1
APPENDIX E	Summary of Lesions in Female Mice in the 2-Year Drinking Water Study of Pyridine	E-1
APPENDIX F	Genetic Toxicology	F-1
APPENDIX G	Hematology and Clinical Chemistry Results	G-1
APPENDIX H	Organ Weights and Organ-Weight-to-Body-Weight Ratios	H-1
APPENDIX I	Reproductive Tissue Evaluations and Estrous Cycle Characterization	I-1
APPENDIX J	Determinations of Pyridine in Plasma	J-1
APPENDIX K	Chemical Characterization and Dose Formulation Studies	K-1
APPENDIX L	Water and Compound Consumption in the 2-Year Drinking Water Studies of Pyridine	L-1
APPENDIX M	Ingredients, Nutrient Composition, and Contaminant Levels in NIH-07 Rat and Mouse Ration	M-1

APPENDIX N	Sentinel Animal Program	N-1
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ABSTRACT



PYRIDINE

CAS No. 110-86-1

Chemical Formula: C_5H_5N Molecular Weight: 79.10

Synonyms: Azabenzene, azine

Pyridine is used as a denaturant in alcohol and antifreeze mixtures, as a solvent for paint, rubber, and polycarbonate resins, and as an intermediate in the manufacture of insecticides, herbicides, and fungicides. It is used in the production of piperidine, an intermediate in the manufacture of rubber and mepiquat chloride, and as an intermediate and solvent in the preparation of vitamins and drugs, dyes, textile water repellants, and flavoring agents in food. Pyridine was nominated for study because of its large production volume and its use in a variety of food, medical, and industrial products. Male and female F344/N rats, male Wistar rats, and male and female B6C3F₁ mice were exposed to pyridine (approximately 99% pure) in drinking water for 13 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, L5178Y mouse lymphoma cells, cultured Chinese hamster ovary cells, *Drosophila melanogaster*, and mouse bone marrow cells.

13-WEEK STUDY IN F344/N RATS

Groups of 10 male and 10 female F344/N rats were exposed to pyridine in drinking water at concentrations of 0, 50, 100, 250, 500, or 1,000 ppm (equivalent to average daily doses of 5, 10, 25, 55, or 90 mg

pyridine/kg body weight). Two females exposed to 1,000 ppm died during week 1. Final mean body weights of 1,000 ppm males and 500 and 1,000 ppm females were significantly less than controls. Water consumption by female rats exposed to 1,000 ppm was less than that by controls. At study termination, evidence of anemia persisted in the 500 and 1,000 ppm males and all exposed groups of females. There was evidence of hepatocellular injury and/or altered hepatic function demonstrated by increases of serum alanine aminotransferase and sorbitol dehydrogenase activity and bile acid concentrations in 500 and 1,000 ppm rats. The estrous cycle length of 1,000 ppm females was significantly longer than that of the controls. Absolute and relative liver weights of males and females exposed to 250, 500, or 1,000 ppm were significantly greater than controls. In the liver, the incidences of centrilobular degeneration, hypertrophy, chronic inflammation, and pigmentation were generally increased in 500 and 1,000 ppm males and females relative to controls. Many of the kidney lesions observed in exposed males are components of spontaneous nephropathy common in male rats including protein casts, chronic inflammation, and mineralization. The severities of renal tubule regeneration increased in male rats exposed to 500 or 1,000 ppm compared to controls. The incidences of granular casts in the kidney and renal tubule hyaline degeneration were increased relative to controls in males exposed to 1,000 ppm.

13-WEEK STUDY IN WISTAR RATS

Groups of 10 male Wistar rats were exposed to pyridine in drinking water at concentrations of 0, 50, 100, 250, 500, or 1,000 ppm (equivalent to average daily doses of 5, 10, 30, 60, or 100 mg/kg). One male rat exposed to 500 ppm died during week 1. Final mean body weights and body weight gains of rats exposed to 250, 500, or 1,000 ppm were significantly less than those of the controls. Water consumption by rats exposed to 1,000 ppm was lower than that by controls. There was evidence of hepatocellular injury and/or altered hepatic function in the 500 and 1,000 ppm groups, similar to that observed in the 13-week study in F344/N rats. Incidences of centrilobular degeneration, hypertrophy, chronic inflammation, and pigmentation in the liver of rats exposed to 500 or 1,000 ppm were significantly increased relative to controls.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female B6C3F₁ mice were exposed to pyridine in drinking water at concentrations of 0, 50, 100, 250, 500, or 1,000 ppm (equivalent to average daily doses of 10, 20, 50, 85, or 160 mg/kg for males and 10, 20, 60, 100, or 190 mg/kg for females). One female mouse exposed to 250 ppm died during week 2. Final mean body weights and body weight gains of female mice exposed to 1,000 ppm were significantly less than those of controls. Water consumption by exposed female mice was lower than that by controls at week 1 but generally slightly higher than controls at week 13. Sperm motility in exposed male mice was significantly decreased relative to controls. Absolute and relative liver weights were significantly increased relative to controls in males exposed to 100 ppm or greater and in 250 and 500 ppm females. No chemical-related lesions were observed in male or female mice.

2-YEAR STUDY IN F344/N RATS

Groups of 50 male and 50 female F344/N rats were exposed to pyridine in drinking water at concentrations of 0, 100, 200, or 400 ppm (equivalent to average daily doses of 7, 14, or 33 mg/kg) for 103 (males) or 104 (females) weeks.

Survival, Body Weights, and Water Consumption

Survival of exposed males and females was similar to that of controls. Mean body weights of 400 ppm males and females were generally less than those of the controls throughout the study, and those of 200 ppm males and females were less than those of controls during the second year of the study. Water consumption by males and females exposed to 200 or 400 ppm was generally greater than that by controls.

Pathology Findings

Incidences of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in male rats exposed to 400 ppm were significantly increased compared to controls and exceeded the historical control ranges. The findings from an extended evaluation (step section) of the kidneys did not reveal additional carcinomas, but additional adenomas were observed in each group of males. In the standard evaluation, an increased incidence of renal tubule hyperplasia was observed in 400 ppm males compared to controls. The severity of nephropathy in males increased slightly with exposure concentration. Incidences of mononuclear cell leukemia in female rats were significantly increased in the 200 and 400 ppm groups compared to controls, and the incidence in the 400 ppm group exceeded the historical control range.

Exposure concentration-related nonneoplastic liver lesions were observed in males and females, and the incidences were generally increased in groups exposed to 400 ppm. These included centrilobular cytomegaly, cytoplasmic vacuolization, periportal fibrosis, fibrosis, centrilobular degeneration and necrosis, and pigmentation. Bile duct hyperplasia occurred more often in exposed females than in controls.

2-YEAR STUDY IN WISTAR RATS

Groups of 50 male Wistar rats were exposed to pyridine in drinking water at concentrations of 0, 100, 200, or 400 ppm (equivalent to average daily doses of 8, 17, or 36 mg/kg) for 103 weeks.

Survival, Body Weights, and Water Consumption

Survival of rats exposed to 200 or 400 ppm was significantly less than that of the controls. Mean body weights of rats exposed to 100, 200, or 400 ppm were significantly less than controls beginning in weeks 69, 49, and 6, respectively. Water consumption by exposed rats was similar to that by controls.

Pathology Findings

The incidence of testicular adenoma in rats exposed to 400 ppm was significantly increased compared to controls. Incidences of interstitial cell hyperplasia were observed in control and exposed groups and were slightly, but not significantly, increased in rats exposed to 200 or 400 ppm.

Severity of nephropathy was marked in all groups, and additional evidence of kidney disease, including mineralization in the glandular stomach, parathyroid gland hyperplasia, and fibrous osteodystrophy, was observed in 100 and 200 ppm rats. Relative to the controls, the incidences of hepatic centrilobular degeneration and necrosis, fibrosis, periportal fibrosis, and/or pigmentation were increased in exposed groups.

2-YEAR STUDY IN MICE

Groups of 50 male B6C3F₁ mice were exposed to pyridine in drinking water at concentrations of 0, 250, 500, or 1,000 ppm (equivalent to average daily doses of 35, 65, or 110 mg/kg) for 104 weeks, and groups of 50 female B6C3F₁ mice were exposed to pyridine in drinking water at concentrations of 0, 125, 250, or 500 ppm (equivalent to average daily doses of 15, 35, or 70 mg/kg) for 105 weeks.

Survival, Body Weights, and Water Consumption

Survival of exposed males and females was similar to that of the controls. Mean body weights of 500 and 1,000 ppm females were less than controls from weeks 89 and 73, respectively. Water consumption by males exposed to 250 or 500 ppm was generally greater than that by controls; male mice exposed to 1,000 ppm consumed less water than controls throughout the study. Water consumption by exposed females was generally lower than that by controls during the first year of the study, but greater than controls during the second year.

Pathology Findings

Hepatocellular neoplasms, including hepatoblastomas, in exposed male and female mice were clearly related to pyridine exposure. Additionally, many mice had multiple hepatocellular neoplasms. The incidences of hepatocellular neoplasms in exposed males and females generally exceeded the historical control ranges for drinking water studies. Neoplasms from control mice, 500 ppm females, and 1,000 ppm males were negative when stained for p53 protein.

GENETIC TOXICOLOGY

Pyridine was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA5137 or in L5178Y mouse lymphoma cells, with or without S9 metabolic activation, and it did not induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells, with or without S9. Pyridine was tested for induction of sex-linked recessive lethal mutations in adult male *Drosophila melanogaster*, and mixed results were obtained. In one experiment, administration by injection gave negative results, but feeding produced an equivocal response. A second experiment generated negative results by injection and feeding. A third experiment showed significant increases in sex-linked recessive lethal mutations in flies treated with pyridine by injection but not by feeding. Results of a single reciprocal translocation test in male *Drosophila melanogaster* were negative. No induction of chromosomal aberrations or micronuclei was noted in bone marrow cells of male mice administered pyridine via intraperitoneal injection.

CONCLUSIONS

Under the conditions of these 2-year drinking water studies, there was *some evidence of carcinogenic activity** of pyridine in male F344/N rats based on increased incidences of renal tubule neoplasms. There was *equivocal evidence of carcinogenic activity* of pyridine in female F344/N rats based on increased incidences of mononuclear cell leukemia. There was *equivocal evidence of carcinogenic activity* in male Wistar rats based on an increased incidence of interstitial cell adenoma of the testis. There was *clear*

evidence of carcinogenic activity of pyridine in male and female B6C3F₁ mice based on increased incidences of malignant hepatocellular neoplasms.

In F344/N rats, exposure to pyridine resulted in increased incidences of centrilobular cytomegaly and degeneration, cytoplasmic vacuolization, and pigmentation in the liver of males and females; periportal fibrosis, fibrosis, and centrilobular necrosis in the liver of males; and bile duct hyperplasia in females. In male Wistar rats, pyridine exposure resulted in increased incidences of centrilobular degeneration and necrosis, fibrosis, periportal fibrosis, and pigmentation in the liver, and secondary to kidney disease, mineralization in the glandular stomach and parathyroid gland hyperplasia.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 16.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Pyridine

	Male F344/N Rats	Female F344/N Rats	Male Wistar Rats	Male B6C3F ₁ Mice	Female B6C3F ₁ Mice
Exposure Concentrations	0, 100, 200, or 400 ppm	0, 100, 200, or 400 ppm	0, 100, 200, or 400 ppm	0, 250, 500, or 1,000 ppm	0, 125, 250, or 500 ppm
Body weights	200 and 400 ppm groups less than controls	200 and 400 ppm groups less than controls	Exposed groups less than controls	Exposed groups similar to controls	Exposed groups less than controls
Survival rates	25/50, 20/50, 25/50, 16/50	32/50, 37/50, 29/50, 26/50	22/50, 14/50, 11/50, 7/50	35/50, 28/50, 35/49, 35/50	32/50, 30/50, 22/50, 29/50
Nonneoplastic effects	<u>Liver</u> : centrilobular cytomegaly (0/50, 4/49, 8/50, 6/50); cytoplasmic vacuolization (4/50, 6/49, 13/50, 17/50); periportal fibrosis (0/50, 0/49, 2/50, 29/50); fibrosis (1/50, 1/49, 1/50, 10/50); centrilobular degeneration (1/50, 3/49, 2/50, 8/50); centrilobular necrosis (0/50, 3/49, 0/50, 5/50); pigmentation (4/50, 11/49, 20/50, 25/50)	<u>Liver</u> : centrilobular cytomegaly (0/50, 1/50, 4/50, 20/50); cytoplasmic vacuolization (10/50, 7/50, 9/50, 18/50); centrilobular degeneration (1/50, 2/50, 2/50, 7/50); bile duct hyperplasia (20/50, 29/50, 34/50, 29/50); pigmentation (6/50, 2/50, 6/50, 17/50)	<u>Liver</u> : centrilobular degeneration (1/50, 15/50, 25/50, 33/50); centrilobular necrosis (5/50, 6/50, 4/50, 23/50); fibrosis (1/50, 5/50, 26/50, 31/50); periportal fibrosis (0/50, 0/50, 5/50, 7/50); pigmentation (6/50, 15/50, 34/50, 42/50) <u>Glandular Stomach</u> : mineralization (8/49, 25/50, 16/48, 6/48) <u>Parathyroid Gland</u> : hyperplasia (16/48, 32/47, 29/48, 12/47)	None	None
Neoplastic effects	<u>Kidney</u> : renal tubule adenoma (standard evaluation - 1/50, 0/48, 2/50, 6/49; standard and extended evaluations combined - 2/50, 3/48, 6/50, 10/49); renal tubule adenoma or carcinoma (standard evaluation - 1/50, 1/48, 2/50, 6/49; standard and extended evaluations combined - 2/50, 4/48, 6/50, 10/49)	None	None	<u>Liver</u> : hepatocellular adenoma (29/50, 40/50, 34/49, 39/50); hepatocellular carcinoma (15/50, 35/50, 41/49, 40/50); hepatoblastoma (2/50, 18/50, 22/49, 15/50); hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (38/50, 47/50, 46/49, 47/50)	<u>Liver</u> : hepatocellular adenoma (37/49, 39/50, 43/50, 34/50); hepatocellular carcinoma (13/49, 23/50, 33/50, 41/50); hepatoblastoma (1/49, 2/50, 9/50, 16/50); hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (41/49, 42/50, 45/50, 44/50)
Uncertain findings	None	<u>All Organs</u> : mononuclear cell leukemia (12/50, 16/50, 22/50, 23/50)	<u>Testis</u> : interstitial cell adenoma (5/50, 6/49, 4/49, 12/50)	None	None

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Pyridine

	Male F344/N Rats	Female F344/N Rats	Male Wistar Rats	Male B6C3F ₁ Mice	Female B6C3F ₁ Mice
Level of evidence of carcinogenic activity	Some evidence	Equivocal evidence	Equivocal evidence	Clear evidence	Clear evidence
Genetic toxicology					
<i>Salmonella typhimurium</i> gene mutations:		Negative in strains TA98, TA100, TA1535, and TA1537, with and without S9			
Mouse lymphoma gene mutations:		Negative with and without S9			
Sister chromatid exchanges					
Cultured Chinese hamster ovary cells <i>in vitro</i> :		Negative with and without S9			
Chromosomal aberrations		Negative with and without S9			
Cultured Chinese hamster ovary cells <i>in vitro</i> :		Negative			
Mouse bone marrow <i>in vivo</i> :		Positive by injection; equivocal by feeding			
Sex-linked recessive lethal mutations					
<i>Drosophila melanogaster</i> :		Negative			
Reciprocal translocations					
<i>Drosophila melanogaster</i> :		Negative			
Micronucleated erythrocytes					
Mouse bone marrow <i>in vivo</i> :					

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

Clear evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

Some evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

Equivocal evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.

No evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.

Inadequate study of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

**NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE**

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on pyridine on 9-10 December 1997 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

to ascertain that all relevant literature data have been adequately cited and interpreted,
to determine if the design and conditions of the NTP studies were appropriate,
to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
to judge the significance of the experimental results by scientific criteria, and
to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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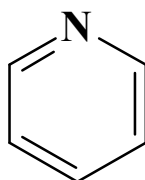
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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

NOTE: A summary of the Technical Reports Review Subcommittee s remarks will appear in a future draft of this report.

INTRODUCTION



PYRIDINE

CAS No. 110-86-1

Chemical Formula: C_5H_5N Molecular Weight: 79.10

Synonyms: Azabenzene, azine

CHEMICAL AND PHYSICAL PROPERTIES

Pyridine is a slightly yellow or colorless, hygroscopic liquid with a characteristic nauseating odor and a burning taste. It is miscible with water, alcohols, diethyl ether, benzene, ligroin, and fatty oils and is slightly alkaline in reaction (pK_a of 5.19). Pyridine boils at approximately 115° C at 760 mm Hg and has a specific gravity of 0.982 at 20°/4° C, a vapor pressure of approximately 20 Torr at 25° C, and a vapor density of 2.73 (Jori *et al.*, 1983; Hawley *s*, 1987; Merck Index, 1989; Lewis, 1993). The liquid has a flash point (closed cup) of 20° C and is flammable when exposed to heat, flame, or oxidizers; the vapor explodes upon contact with a flame or spark. When heated to decomposition, it emits cyanide fumes (Hawley *s*, 1987; Sittig, 1991; Lewis, 1993).

PRODUCTION, USE, AND HUMAN EXPOSURE

Pyridine is produced by coal carbonization and recovery from coke-oven gases and coal tar middle oil. Since the 1950s, it has also been produced synthetically from the vapor phase reaction of acetaldehyde and

ammonia, with formaldehyde and methanol sometimes added (Jori *et al.*, 1983; NCI, 1985).

Pyridine is a solvent that is widely employed in industry and the laboratory. It is used as a denaturant in alcohol and antifreeze mixtures, as a solvent for paint, rubber, and polycarbonate resins, and as an intermediate in the manufacture of insecticides (chlorpyrifos), herbicides (paraquat and trichloropyr), and fungicides. It is used in the production of piperidine, an intermediate in the manufacture of rubber and mepiquat chloride. Pyridine is also used as an intermediate and solvent in the preparation of vitamins and drugs, dyes, textile water repellants, and flavoring agents in food (NCI, 1985; Hawley *s*, 1987; ATSDR, 1992).

Manufacturers and consumers used an estimated 300,000 kg pyridine in 1977. Approximately 4.5 to 8.9×10^6 kg pyridine was produced in the United States in 1975, 27×10^6 kg in 1976, and 11.6×10^6 kg in 1978 (Pyridine Task Force, correspondence from Chairmen to U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC, 1978). No information on the current annual production of pyridine is available in the literature (ATSDR, 1992).

The greatest potential for exposure to pyridine is in the workplace. Occupational exposures, usually by inhalation or dermal absorption, may occur during pyridine production or its use as a chemical intermediate or solvent (NCI, 1985). Exposure may also occur at coke-oven and oil-shale processing facilities. The EPA (USEPA, 1978) estimated that 249,000 persons were occupationally exposed to pyridine. NIOSH estimated the extent of potential human exposure between 1981 and 1983 at over 41,000 workers (NIOSH, 1990). The 8-hour, time-weighted, average permissible exposure level for pyridine is 5 ppm (16 mg/m^3) (ACGIH, 1997). NIOSH (1985) determined the concentration immediately dangerous to life or health to be 3,600 ppm. The pungent odor of pyridine (odor threshold of 0.17 ppm in air) serves to limit voluntary exposure (NCI, 1985). The odor becomes objectionable to unaccustomed individuals at 10 ppm, and olfactory fatigue occurs at greater than 5 ppm (Jori *et al.*, 1983).

Pyridine has rarely been detected in ambient air, water, or soil except near industrial sources (ATSDR, 1992). Pyridine is released into the atmosphere as fugitive emissions from coal gasification and oil shale processing facilities, from ironworking and coking plants (Masek, 1981), and from the combustion of polyisocyanate foam products (Seader *et al.*, 1972; Junk and Ford, 1980); an estimated 298,438 pounds of pyridine were released in air, 4,630 pounds in surface water, and 303,650 pounds in groundwater in 1987 (ATSDR, 1992). In addition, 209,880 pounds of pyridine were disposed of in publicly owned wastewater treatment plants (ATSDR, 1992). Pyridine has been identified in effluent from wastewater treatment plants (Ellis *et al.*, 1982), natural waters (Shelton and Hites, 1978), and groundwater near an underground coal gasification site (Stuermer *et al.*, 1982). Pyridine releases to land from industrial sources were estimated at 28,656 pounds in 1987 (ATSDR, 1992). Many states have regulations concerning the acceptable ambient air concentrations of pyridine. For an 8-hour period, ambient air limits have been set at 300 $\mu\text{g}/\text{m}^3$ in Connecticut, 150 $\mu\text{g}/\text{m}^3$ in Indiana, 0.357 $\mu\text{g}/\text{m}^3$ in Nevada, 0.3 $\mu\text{g}/\text{m}^3$ in Tampa, Florida, and 0.15 $\mu\text{g}/\text{m}^3$ in Vermont. Eighteen- and 24-hour limits have been set at 0.30 $\mu\text{g}/\text{m}^3$ and 250 $\mu\text{g}/\text{m}^3$ in North Dakota and Virginia, respectively, and annual limits have been set at 2.0 $\mu\text{g}/\text{m}^3$ in New York and 35.7 $\mu\text{g}/\text{m}^3$ in Kansas (NATICH, 1989).

In the United States, the general population may be exposed to low concentrations of pyridine by the ingestion of foods. Pyridine was detected among the natural volatile components of several foods, including fried chicken, cheese, fried bacon, and other foods (ATSDR, 1992). The U.S. Environmental Protection Agency (EPA) estimated the ingestion of pyridine in the United States to be about 500 mg per person per year, mainly from food (USEPA, 1978). The Food and Drug Administration has approved the use of pyridine as a flavoring agent (21 CFR 172.515). It is also a coffee aroma constituent (ATSDR, 1992). Pyridine has been identified as a component of tobacco and marijuana smoke (Schmeltz and Hoffmann, 1977; Schumacher *et al.*, 1977; Meril *et al.*, 1981; Curvall *et al.*, 1984; Eatough *et al.*, 1989); the concentration of pyridine in indoor air contaminated with cigarette smoke may be as high as 16 $\mu\text{g}/\text{m}^3$ (ATSDR, 1992).

REGULATORY STATUS

The EPA Office of Toxic Substances has included pyridine in its toxic chemical release reporting rule (40 CFR 372), its health and safety data reporting rule (40 CFR 716.120), and its preliminary assessment information reporting rule (40 CFR 712.30). The annual reportable quantity of pyridine release to the environment has been set at 1,000 pounds by the EPA Office of Emergency and Remedial Response (40 CFR 302.4). The EPA Office of Solid Wastes has listed pyridine as a constituent of hazardous waste (40 CFR 261), monitors its levels in groundwater (40 CFR 264), and restricts its disposal on land (40 CFR 268).

ENVIRONMENTAL IMPACT

Pyridine exists in the atmosphere as a vapor. Atmospheric pyridine may be slowly photodegraded by hydroxyl radicals in the troposphere; the estimated atmospheric life-time is 23 to 46 days. A large fraction of the atmospheric pyridine vapor phase would tend to dissolve in water vapor (clouds and rain) due to its high water solubility. The magnitude of the Henry's law constant for aqueous solutions of pyridine indicates that much of the atmospheric pyridine is removed by precipitation and suggests that the pyridine in water does not volatilize readily into the atmosphere. The volatility and sorption of pyridine from water varies considerably and is pH dependent. The rate of removal of pyridine from unfiltered river water by biodegradation depends on the initial pyridine concentration. At concentrations less than 20 mg/L, pyridine degradation was virtually complete in 8 days or less. Pyridine in water may partition to soils and sediments to an extent that depends on the pH of the water and the organic carbon content of the soil. Due to its low carbon/water partition coefficient, pyridine is highly mobile in soil. In laboratory screening tests, however, about 94% to 100% of the pyridine added to municipal wastewater biodegraded in 2 to 21 days (ATSDR, 1992).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Pyridine is absorbed by inhalation and by oral or dermal exposure. Pyridine is eliminated in exhaled air, feces, and urine as free base and/or metabolites (Jori *et al.*, 1983; NCI, 1985).

Pyridine is metabolized primarily by N-methylation and/or aromatic hydroxylation; urinary excretion of metabolites and unchanged compound is the major route of elimination (NCI, 1985). The metabolic pathway in Figure 1 incorporates all the major urinary metabolites of pyridine that have been identified (ATSDR, 1992).

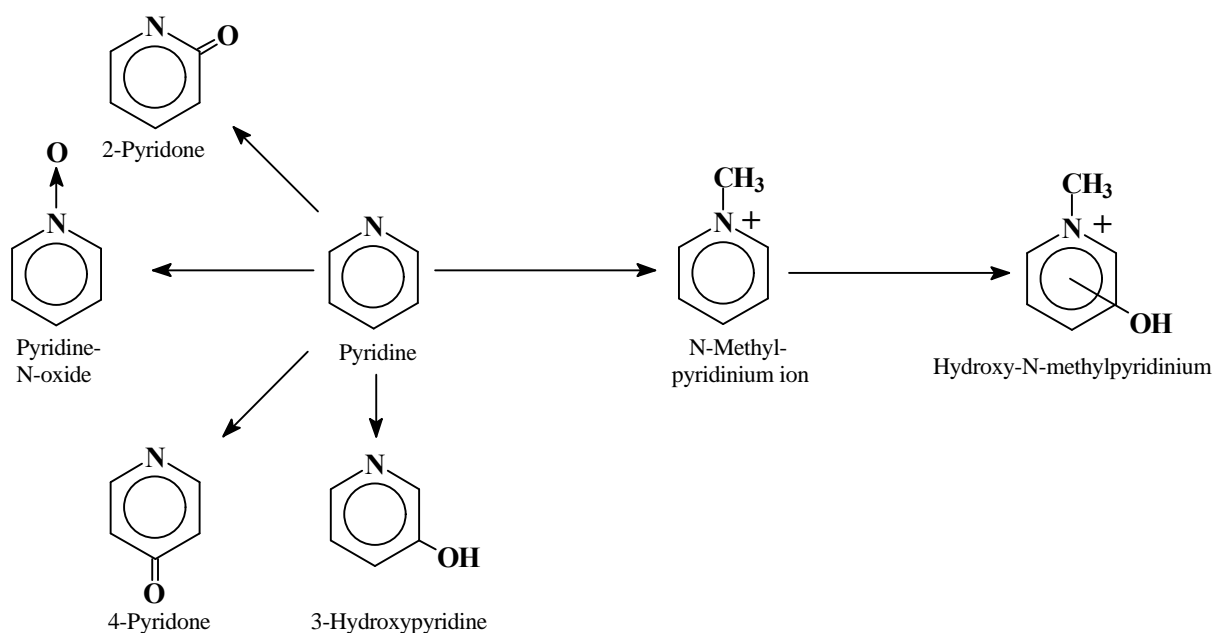


FIGURE 1
Proposed Metabolic Pathway for Pyridine

Experimental Animals

In a series of studies on pyridine N-methylation by D Souza *et al.* (1980), a single 7 mg [¹⁴C]-pyridine/kg dose was administered by intraperitoneal injection to groups of one to five female Wistar albino rats, female Tuck strain mice, male and female Dunkin-Hartley guinea pigs, female gerbils, female golden Syrian hamsters, male and female New Zealand White rabbits, and mongrel female cats. In the rat, mouse, guinea pig, gerbil, and hamster, 48% to 67% of the administered radiolabel was recovered in the urine within 24 hours. In the cat and rabbit, 75% and 77% were recovered at 48 and 72 hours, respectively. Pyridine N-methylation was extensive (15% to 40% of the administered dose) in the guinea pig, gerbil,

hamster, rabbit, and cat and lower (approximately 5% to 12%) in the rat and mouse. To determine whether the N-methylpyridinium ion formed during the metabolism of pyridine is further metabolized, groups of three female rats and guinea pigs were injected intraperitoneally with 8 mg/kg N-methyl[2,6- ^{14}C]-pyridinium as an aqueous solution of the iodide. Greater than 95% of the radiolabel recovered in the urine (rats, 53%; guinea pigs, 85%) was unchanged compound, indicating that N-methylpyridinium is largely metabolically stable (D Souza *et al.*, 1980).

The effects of route of administration, dose, and methionine supplementation on the N-methylation of pyridine were also investigated by D Souza *et al.* (1980) in the rat (a poor pyridine methylator) and guinea pig (a good pyridine methylator). [^{14}C]-Pyridine was administered orally at doses of 7, 68, or 357 mg/kg or intraperitoneally at doses of 1, 7, or 500 mg/kg to groups of three animals. N-Methylation of pyridine was found to be independent of the route of administration, but dependent on the dose. In rats given 7 mg/kg [^{14}C]-pyridine orally, 58% of the total ^{14}C was excreted within 24 hours, with 3.1% of the dose as the N-methylpyridinium ion; 48% of the total ^{14}C was excreted within 24 hours following intraperitoneal injection of 7 mg/kg, with 5.0% of the dose as N-methylpyridinium ion. In the guinea pig, 31% of the administered dose was recovered in the urine as the N-methylpyridinium ion, regardless of the route of administration (recovery of orally and intraperitoneally administered total ^{14}C was 76% and 66%, respectively). In contrast, a study by Okuda (1959) demonstrated that 2.5 times more N-methylpyridine was produced following subcutaneous administration than following oral administration of pyridine to dogs.

For both the rat and guinea pig (D Souza *et al.*, 1980), overall urinary recovery of ^{14}C was inversely proportional to the dose. The metabolic reaction was saturable in both species. In another experiment (D Souza *et al.*, 1980), rats were pretreated with an injection of 1 g/kg DL-methionine 24 hours prior to administration of 7 mg/kg [^{14}C]-pyridine and then maintained on a diet enriched with DL-methionine. The excretion of total ^{14}C and N-methylpyridinium ion were unaffected by methionine supplementation, which demonstrated that low N-methylation in the rat is unrelated to a relative deficiency of source methyl groups. In these same cross-species studies, Damani *et al.* (1982) identified 2-pyridine,

3-hydroxypyridine, and 4-pyridone in the urine of all species and pyridine N-oxide in all species except the rabbit, although the relative amounts of metabolites differed across species. In hamsters, guinea pigs, and cats, most of the urinary radioactivity was identified as unchanged pyridine and its C- and N-oxidation and N-methylated derivatives. A significant proportion of the excreted radioactivity in rats, gerbils, and rabbits could not be accounted for by the metabolites monitored in these studies, but 3-hydroxypyridine (not measured) was probably represented in the urine in a conjugated form. In rats, an unidentified cationic metabolite accounted for about 7.4% of the recovered radiolabel (Damani *et al.*, 1982).

D Souza *et al.* (1980) suggested that N-methylation and quaternization of pyridine may result in the formation of a conjugation product (the N-methylpyridinium ion) more toxic than pyridine itself. The intraperitoneal LD₅₀ for N-methylpyridinium ion in mice is 0.22 g/kg, compared to 1.2 g/kg for pyridine. Production of N-oxides, generally associated with detoxification and increased elimination in several animal species and humans, may conceivably result in an increase in toxicity or carcinogenicity, and the N-oxidation of pyridine may represent a route for bioactivation (NCI, 1985; Kim *et al.*, 1991a).

Pyridine, which is metabolized by cytochromes P2E1 and P4B (CYP2E1 and CYP4B), enhances the expression of various hepatic P₄₅₀ isozymes in rats and rabbits (Kim and Novak, 1990; Kim *et al.*, 1991a; Kim *et al.*, 1993; Nikula *et al.*, 1995). The studies of Kim *et al.* (1991a) demonstrated that pyridine enhances the expression of different gene subfamilies of rat hepatic cytochrome P₄₅₀ including CYP2E1, CYP1A1, CYP1A2, CYP2B1, and CYP2B2 (Kim and Novak, 1990; Kim *et al.*, 1991b; Hotchkiss *et al.*, 1993; Iba *et al.*, 1993; Agarwal *et al.*, 1994).

Pyridine caused a dose-dependent, 4- to 22-fold elevation of hepatic CYP2B1/2B2 over the intraperitoneal dosing regimen of 100 to 400 mg/kg per day in Sprague-Dawley rats. Pyridine treatment increased CYP2B1 and CYP2B2 poly (A)+ RNA levels approximately 69- and 34-fold, respectively, while CYP2E poly (A)+ levels failed to increase (Kim *et al.*, 1993). Pyridine is similar to phenobarbital (Lubet *et al.*, 1989) and oxazepam (Griffin *et al.*, 1995) in this induction of CYP2B enzymes. Lubet *et al.* (1989) have associated the strength of this CYP2B induction response to the strength of liver neoplasm promotion in the

rat, although the mechanisms are not known. Rice *et al.* (1994) have also studied the association between CYP2B induction and liver neoplasm-promoting activity in the rat, and while there is a correlation with an induction of CYP2B and liver neoplasm promotion (after initiation with N-nitrosodiethylamine), other factors may be involved. Chemicals such as phenobarbital, which induces cytochrome P₄₅₀s in the rodent liver, induce a wide variety of enzyme systems (referred to as pleiotropic response), and it is likely that several effects of the chemical play a role in its liver neoplasm-promoting ability (McClain, 1990).

Humans

N-Methylpyridinium ion (5.5% and 12% of the dose) was present in urine collected 24 hours after two human volunteers received 3.4 mg [¹⁴C]-pyridine in orange juice (approximately 0.05 mg/kg) (D Souza *et al.*, 1980). Pyridine-N-oxide was identified as a metabolite in the urine sample, accounting for 32% of the administered dose (Damani *et al.*, 1982). Approximately 25% of the urinary metabolites were not identified.

Pyridine and a number of its derivatives have been shown to cause selective inhibition of thromboxane synthetase *in vitro* in fresh citrated human blood (Miyamoto *et al.*, 1980) and in a test system employing the microsomal fraction of human platelet microsomes (Tai *et al.*, 1980); thromboxane A₂ is a potent labile inducer of platelet aggregation and vascular constriction. The inhibitory potency of pyridine on thromboxane synthetase in these systems was 60 μ M in blood and 270 μ M in platelet microsomes. In addition, pyridine (1.5 mM) inhibited the aggregation of human platelets induced by arachidonic acid or adenosine triphosphate (Tai *et al.*, 1980).

TOXICITY

Experimental Animals

Reported pyridine LD₅₀/LC₅₀ values for rats are 891 to 1,580 mg/kg (oral), 360 mg/kg (intravenous), 866 to 1,150 mg/kg (subcutaneous), and approximately 8,000 to 9,000 ppm for 1 hour (inhalation) (Vernot *et*

al., 1977; Jori *et al.*, 1983; ATSDR, 1992). LD₅₀ values for mice are 1,500 mg/kg (oral), 1,200 mg/kg (intraperitoneal), 420 mg/kg (intravenous), and 1,250 mg/kg (subcutaneous) (Jori *et al.*, 1983).

Pyridine has been reported to cause toxic effects in the liver and kidney in experimental animal model systems. Pyridine administration (oral gavage) to dogs has produced toxic effects in the liver and kidney (Jori *et al.*, 1983). Decreased glutamine concentration and increased ammonia excretion were observed in rats (age and strain not specified) exposed to pyridine vapors at a concentration of 5 to 10 mg/L for a single 40-minute exposure (ATSDR, 1992).

In a study in Sprague-Dawley rats (Anderson, 1987), pyridine was administered by gavage at 0, 0.24, 1, 10, 25, or 50 mg/kg per day in water for 90 consecutive days. No treatment-related deaths occurred during the study. Body weights relative to controls were significantly reduced in male rats in the 50 mg/kg per day group. A dose-related mildly elevated serum cholesterol occurred in females at 25 and 50 mg/kg per day on days 30 and 90, and female rats that received 10 mg/kg or greater had significantly increased liver weights. Mild inflammatory hepatic lesions were seen in 70% of males and 20% of females in the 50 mg/kg groups; the incidence of inflammatory hepatic lesions was 10% in male and female control groups. Lesions included mixed peribiliary infiltrate, bile ductule proliferation, enlarged and vacuolated hepatocytes, and necrosis of hepatocytes. Liver lesions also occurred in the 10 and 25 mg/kg groups.

In a study in which rats were given subcutaneous injections of pyridine twice weekly for a year at doses of 3, 10, 30, or 100 mg/kg (Mason *et al.*, 1971), survival rates and neoplasm incidences in pyridine-treated rats were similar to those in the controls. Mean body weights of the dosed groups ranged from 84% to 95% of those of the controls at the end of the study.

Inhalation of 5 or 444 ppm pyridine 6 hours per day for 4 days was associated with olfactory epithelial lesions in the nasal mucosa of male F344/N rats characterized by vacuolar degeneration of sustentacular cells, focal, marked attenuation of the epithelium, loss of sensory neurons, and intraepithelial luminal

structures (Nikula and Lewis, 1994). These lesions were associated with induction of carboxylesterase (Nikula *et al.*, 1995).

Humans

There are no adequate studies on the toxicity of pyridine in humans. Several reports indicate that pyridine may be moderately toxic by the oral, dermal, intravenous, and inhalation routes. The chemical can cause skin irritation and severe eye damage (Sittig, 1991; Lewis, 1993).

In a review of the literature on pyridine, ATSDR (1992) reported the death of a man receiving pyridine as an intermittent medication for the treatment of epilepsy. The patient was also taking other medications (including phenobarbital), and it was not possible to attribute this death specifically to pyridine.

A 29-year-old man who accidentally swallowed ½ cup (approximately 125 mL) of pyridine experienced nausea, dizziness, abdominal pain, and lung congestion followed by death within 2 days (Jori *et al.*, 1983).

Inhalation is a primary route of exposure to pyridine, and mild symptoms of central nervous system injury may result from exposure to approximately 10 ppm (Jori *et al.*, 1983; NCI, 1985). Similar symptoms (headache, dizziness, insomnia, nausea, and anorexia) were reported in workers exposed to 125 ppm pyridine, 4 hours per day for 1 to 2 weeks (Jori *et al.*, 1983).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Injection of 10 or 20 mg pyridine into eggs caused muscular hypoplasia in 15% and 67% of chicks, respectively. The 20 mg dose induced defective beaks in 4.9% of the chicks and short or twisted necks in 1.1% (ATSDR, 1992). No information related to the reproductive or developmental toxicity of pyridine in humans was found in a search of the available literature.

CARCINOGENICITY

No information related to the carcinogenicity of pyridine in experimental animals or humans was found in a search of the available literature.

GENETIC TOXICITY

Pyridine has been tested in a variety of *in vivo* and *in vitro* assays, and with few exceptions, results were negative. No mutation induction (Pai *et al.*, 1978) or growth inhibition due to DNA damage was noted in *Escherichia coli* after treatment with pyridine (Warren *et al.*, 1981; Riebe *et al.*, 1982). No increases in gene mutation frequencies were observed in a variety of *Salmonella typhimurium* strains exposed to pyridine in the presence or the absence of S9 activation enzymes (Florin *et al.*, 1980; Kawachi *et al.*, 1980; Warren *et al.*, 1981; Riebe *et al.*, 1982; Haworth *et al.*, 1983). Zimmermann *et al.* (1986) reported induction of aneuploidy in *S. cerevisiae* D61.M after treatment with up to 1.1% pyridine, presumably resulting from disruption of microtubule assembly processes. No significant increases in mutant frequencies were seen in L5178Y mouse lymphoma cell cultures after incubation with pyridine, with or without S9 activation (McGregor *et al.*, 1988). There are two published data sets from *Drosophila melanogaster* sex-linked recessive lethal assays with pyridine, and the results are mixed. Valencia *et al.* (1985) reported negative results when pyridine was administered to adult male flies by injection (7,000 ppm) and equivocal results when feeding (700 ppm) was used as the route of administration. Mason *et al.* (1992) reported negative results in a sex-linked recessive lethal assay from a feeding study (500 ppm) but positive results after injection of 4,300 ppm pyridine. This positive result with pyridine in the sex-linked recessive lethal assay was followed by a test for induction of reciprocal translocations in male *Drosophila*, and negative results were obtained in this assay (Mason *et al.*, 1992).

Cytogenetic investigations in mammalian test systems yielded negative results with pyridine for induction of chromosomal aberrations (Abe and Sasaki, 1977; Ishidate and Odashima, 1977; Kawachi *et al.*, 1980)

and sister chromatid exchanges (Abe and Sasaki, 1977; Kawachi *et al.*, 1980) in cultured Chinese hamster ovary cells, tested in the absence of S9 activation enzymes. *In vivo*, no induction of micronuclei in mouse bone marrow cells (Harper *et al.*, 1984) or chromosomal aberrations in rat bone marrow cells was reported after treatment with pyridine.

There are little mutagenicity data for metabolites of pyridine. Pyridine-1-oxide was negative in bacterial tests for gene mutation induction (Voogd *et al.*, 1980) or growth inhibition due to DNA damage (Nagao and Sugimura, 1972), and it did not produce growth inhibition secondary to DNA damage in *S. cerevisiae* (Nagao and Sugimura, 1972). These tests were conducted without S9. 3-Hydroxypyridine, another pyridine metabolite, did not cause gene reversion in *S. typhimurium*, with or without S9 (Florin *et al.*, 1980).

In summary, there appears to be little evidence to indicate that pyridine is mutagenic in standard short-term tests.

STUDY RATIONALE

Pyridine was tested by the National Toxicology Program because of the large amount produced and its use in a variety of industrial products. The oral route of administration was selected to evaluate the systemic effects of pyridine. Pyridine has been shown to increase the severity of leukemia in a transplant model for leukemia in male F344/N rats (Dieter *et al.*, 1989), and male Wistar rats were added to these studies in order to evaluate the effects of pyridine in a rat model with a low spontaneous incidence of mononuclear cell leukemia.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PYRIDINE

Pyridine was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (00103BV). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix K). Reports on analyses performed in support of the pyridine studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear, colorless liquid, was identified as pyridine by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of lot 00103BV was determined by elemental analyses, Karl Fischer water analysis, functional group titration, and gas chromatography. Elemental analyses for hydrogen and nitrogen were in agreement with the theoretical values for pyridine; results for carbon were slightly low. Karl Fischer water analysis indicated $0.049\% \pm 0.003\%$ water. Functional group titration indicated a purity of $99.8\% \pm 0.6\%$. Gas chromatography indicated one major peak and no impurities with an area greater than or equal to 0.1% relative to the major peak area in two systems. The overall purity was determined to be greater than 99%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using gas chromatography. To ensure stability, the bulk chemical was stored at 1° C to 8° C in amber glass bottles in the dark. Stability was monitored during the 13-week and 2-year studies using gas chromatography. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared as needed by mixing pyridine with deionized water (Table K1).

Stability studies of a 0.01 mg/mL formulation were performed by the analytical chemistry laboratory using high-performance liquid chromatography. The stability of the dose formulation was confirmed for at least 3 weeks when stored in the dark at room temperature.

Periodic analyses of the dose formulations of pyridine were conducted at the study laboratory and analytical chemistry laboratory using high-performance liquid chromatography. For the 13-week studies, dose formulations were analyzed after preparation at the beginning, midpoint, and end of the studies (Table K2). During the 2-year studies, dose formulations were analyzed approximately every 6 to 10 weeks (Table K3). All dose formulations analyzed and used during the 13-week studies (45/45) were within 10% of the target concentration. Of the dose formulations analyzed during the 2-year studies, 99% (191/192) were within 10% of the target concentration. One formulation was 47% less than the target concentration; because records indicated that the proper amounts of pyridine and deionized water were used, it is possible that the wrong dose formulation was sampled for analysis. This dose formulation was remixed, and the remix was found to be within 10% of the target concentration. All animal room samples (75/75) were within 10% of the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory during the 13-week studies agreed with the results obtained by the study laboratory (Table K4).

13-WEEK STUDIES

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to pyridine and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F₁ mice were obtained from Taconic Farms (Germantown, NY); male Wistar rats were obtained from Charles River Laboratories (Kingston, NY). On receipt, rats and mice

were approximately 5 weeks old. Animals were quarantined for 12 to 14 days and were 7 or 8 weeks old on the first day of the studies. Before initiation of the studies, five male and five female F344/N rats and mice and five male Wistar rats were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female sentinel F344/N rats and mice and five male sentinel Wistar rats using the protocols of the NTP Sentinel Animal Program (Appendix N).

Groups of 10 male and 10 female F344/N rats and B6C3F₁ mice and 10 male Wistar rats were given drinking water containing 0, 50, 100, 250, 500, or 1,000 ppm pyridine (core study). Groups of 10 male and 10 female F344/N rats and 10 male Wistar rats exposed to the same concentrations were designated as special study animals for hematology and clinical chemistry analyses. Feed and water were available *ad libitum*; fresh control or treated water was provided twice weekly. F344/N and Wistar rats were housed five per cage, and mice were housed individually. Clinical findings were recorded weekly for rats and mice. Water consumption was recorded twice weekly by cage for core study animals. The animals were weighed initially and weekly thereafter. Details of the study design and animal maintenance are summarized in Table 1.

Blood was collected from the retroorbital sinus of special study F344/N rats and Wistar rats on days 5 and 20 and of core study rats at study termination for hematology and clinical chemistry analyses.

Erythrocyte, leukocyte, and platelet counts; hemoglobin concentration; hematocrit, mean cell volume; mean cell hemoglobin; and mean cell hemoglobin concentration were measured with a Sysmex TOA E-2500. Blood smears were stained with Wright/Giemsa; differential leukocyte counts were based on classifying a minimum of 100 cells. Reticulocyte counts were done on a smear prepared from whole blood mixed with new methylene blue N stain and incubated at room temperature; 1,000 erythrocytes were counted and the percent reticulocytes was determined. Clinical chemistry analyses were performed on the Roche Cobas FARA automated centrifugal analyzer (Roche Diagnostic Systems, Inc., Montclair, NJ). The hematology and clinical chemistry parameters measured are listed in Table 1.

At the end of the 13-week studies, blood was collected from the retroorbital sinus of all rats for plasma pyridine concentration measurements. Pilot studies determined that samples could be collected between 8 a.m. and 10 a.m. The samples were taken in silicon-coated tubes which contained buffered sodium citrate. A plasma analysis procedure was developed and evaluated at the study laboratory for the analysis of plasma pyridine concentrations ranging from 0.063 to 100 $\mu\text{g/mL}$. Concentrations less than the experimental level of quantitation (ELOQ=0.63 $\mu\text{g/mL}$) should be considered approximations. Plasma samples were treated with sodium hydroxide and 3-methylpyridine, the internal standard. The samples were extracted with dichloromethane, then analyzed using gas chromatography with nitrogen-phosphorous detection. The gas chromatography was performed on a 20% Carbowax 20M-TPA on 80/100 Chromosorb column, with a nitrogen carrier gas at a flow rate of 30 mL/minute, and an oven temperature of 89° C for 7 minutes, then to 170° C at 20° C per minute, with a 2-minute hold. Three standard curve ranges were used to encompass the 1,600-fold quantitation range. Results from these analyses are presented in Appendix J.

At the end of the 13-week studies, samples were collected for sperm motility and vaginal cytology evaluations on F344/N rats and mice exposed to 0, 250, 500, or 1,000 ppm. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1987). For 12 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left testis and left epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides, and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae

were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

A necropsy was performed on all core study animals. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μ m, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on control and 1,000 ppm F344/N rats, male Wistar rats, and mice, and target organs were examined to the no-effect level. Table 1 lists the tissues and organs routinely examined. α 2u-Globulin immunohistochemistry, using a primary antibody from Hazleton Laboratories, was done on selected animals from each exposure group.

2-YEAR STUDIES

Study Design

Groups of 50 male and 50 female F344/N rats and 50 male Wistar rats were given drinking water containing 0, 100, 200, or 400 ppm pyridine for 103 (males) or 104 (females) weeks. Groups of 50 male B6C3F₁ mice were exposed to 0, 250, 500, or 1,000 ppm pyridine in drinking water for 104 weeks, and groups of 50 female B6C3F₁ mice were exposed to 0, 125, 250, or 500 ppm pyridine in drinking water for 105 weeks.

Source and Specification of Animals

Male and female F344/N rats and B6C3F₁ mice were obtained from Taconic Farms (Germantown, NY), and male Wistar rats were obtained from Charles River Laboratories (Portage, MI) for use in the 2-year studies. Rats and mice were quarantined for 12 to 14 days before the beginning of the studies. Five male and five female F344/N rats and mice and five male Wistar rats were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 7 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix N).

Animal Maintenance

F344/N rats were housed five per cage, male Wistar rats were housed three per cage, and mice were housed individually. Feed and water were available *ad libitum*. Water consumption was measured weekly by cage for the first 13 weeks and every 4 weeks thereafter. Cages and racks were rotated every two weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix M.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded at 4-week intervals, and body weights were recorded at the start of the study, weekly for the first 13 weeks, every 4 weeks until week 92 (F344/N rats), week 88 (male Wistar rats), or week 96 (mice), and then once every 2 weeks until study termination.

A complete necropsy and microscopic examination were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm , and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ were examined. For extended

evaluation of renal proliferative lesions in male rats, kidneys were step sectioned at 1-mm intervals, and four additional sections were obtained from each kidney. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year rat studies, a quality assessment pathologist reviewed the liver and kidney of male F344/N rats, the liver of female F344/N rats, and the liver, kidney, and testis of male Wistar rats, and all neoplasms in all tissues. For the 2-year mouse studies, a quality assessment pathologist reviewed the liver, nose, and spleen of male and female mice, the adrenal cortex and lung of male mice, the ovary and pituitary gland of female mice, and all neoplasms in all tissues.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data,

the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al.* (1986).

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Pyridine

13-Week Studies	2-Year Studies
Study Laboratory TSI Mason Research Institute (Worcester, MA)	TSI Mason Laboratories (Worcester, MA)
Strain and Species Rats: F344/N and Wistar Mice: B6C3F ₁	Rats: F344/N and Wistar Mice: B6C3F ₁
Animal Source F344/N rats: Taconic Farms (Germantown, NY) Wistar rats: Charles River Laboratories (Kingston, NY) Mice: Taconic Farms (Germantown, NY)	F344/N rats: Taconic Farms (Germantown, NY) Wistar rats: Charles River Laboratories (Portage, MI) Mice: Taconic Farms (Germantown, NY)
Time Held Before Studies F344/N rats: 14 days (males) or 12 days (females) Wistar rats: 13 days Mice: 13 days (males) or 14 days (females)	F344/N rats: 12 days (males) or 13 days (females) Wistar rats: 13 days Mice: 13 days (males) or 14 days (females)
Average Age When Studies Began 7 weeks, except special study F344/N rats at 8 weeks	7 weeks
Date of First Exposure Core Studies: F344/N rats: 24 January (males) or 22 January (females) 1990 Wistar rats: 28 February 1990 Mice: 20 December (males) or 21 December (females) 1989 Special Studies: F344/N rats: 3 February (males) or 1 February (females) 1990 Wistar rats: 1 March 1990	F344/N rats: 23 April (males) or 24 April (females) 1991 Wistar rats: 14 May 1991 Mice: 3 April (males) or 4 April (females) 1991
Duration of Exposure 13 weeks (core study animals) 19 days (special study F344/N rats) 20 days (special study Wistar rats)	F344/N and Wistar rats: 103 weeks (males) or 104 weeks (females) Mice: 104 weeks (males) or 105 weeks (females)
Date of Last Exposure Core Studies: F344/N rats: 25 April (males) or 23 April (females) 1990 Wistar rats: 30 May 1990 Mice: 21 March (males) or 22 March (females) 1990 Special Studies: F344/N rats: 22 February (males) or 20 February (females) 1990 Wistar rats: 20 March 1990	F344/N rats: 13 April (males) or 22 April (females) 1993 Wistar rats: 4 May 1993 Mice: 25 March (males) or 1 April (females) 1993
Necropsy Dates F344/N rats: 25 April (males) or 23 April (females) 1990 Wistar rats: 30 May 1990 Mice: 21 March (males) or 22 March (females) 1990	F344/N rats: 13 April (males) or 20-22 April (females) 1993 Wistar rats: 4 May 1993 Mice: 23-25 March (males) or 1 April (females) 1993
Average Age at Necropsy 20 weeks (core study)	F344/N and Wistar rats: 110 weeks (males) or 111 weeks (females) Mice: 111 weeks (males) or 112 weeks (females)
Size of Study Groups F344/N rats and mice: 10 males and 10 females Wistar rats: 10 males	F344/N rats and mice: 50 males and 50 females Wistar rats: 50 males
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 13-week studies
Animals per Cage F344/N and Wistar rats: 5 Mice: 1	F344/N rats: 5 Wistar rats: 3 Mice: 1

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Pyridine

13-Week Studies	2-Year Studies
Method of Animal Identification	
Tail tattoo	Tail tattoo
Diet	
NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available <i>ad libitum</i>	Same as 13-week studies
Water	
Deionized water via glass water bottles with stainless steel sipper tubes, available <i>ad libitum</i> , changed twice per week	Same as 13-week studies
Cages	
See-Through Systems polycarbonate, solid bottom (Lab Products, Inc., Rochelle Park, NJ), changed twice per week (rats) or weekly (mice)	Same as 13-week studies, except changed three times per week for male rats
Bedding	
F344/N and Wistar rats: Sani Chips (P.J. Murphy Products Corp., Montville, NJ), changed twice per week Mice: Beta Chips (P.J. Murphy Products Corp., Montville, NJ), changed weekly	Heat-treated hardwood chips (P.J. Murphy Forest Products, Montville, NJ), changed three times per week (male rats), twice per week (female rats), or weekly (mice)
Cage Filters	
Nonwoven fiber (Snow Filtration, Cincinnati, OH), changed once every 2 weeks	Same as 13-week studies
Racks	
Stainless steel (Lab Products, Inc., Rochelle Park, NJ), changed once every 2 weeks	Same as 13-week studies
Animal Room Environment	
Temperature: 20.6°-23.9° C (F344/N rats); 18.9°-23.3° C (Wistar rats); 20.6°-24.4° C (mice) Relative humidity: 31%-57% (F344/N rats); 35%-56% (Wistar rats); 26%-49% (mice) Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 19.4°-24.4° C (F344/N rats); 18.9°-26.7° C (Wistar rats); 20.0°-24.4° C (mice) Relative humidity: 24%-71% (F344/N rats); 25%-78% (Wistar rats); 20%-65% (mice) Room fluorescent light: 12 hours/day Room air changes: 10/hour
Exposure Concentrations	
0, 50, 100, 250, 500, or 1,000 ppm	F344/N and Wistar rats: 0, 100, 200, or 400 ppm Mice: 0, 250, 500, or 1,000 ppm (males); 0, 125, 250, or 500 ppm (females)
Type and Frequency of Observation	
Observed twice daily; animals were weighed initially and weekly thereafter; clinical findings were recorded weekly. Water consumption was recorded twice per week by cage.	Observed twice daily; animals were weighed initially, weekly for the first 13 weeks, every 4 weeks until week 92 (F344/N rats), week 88 (Wistar rats), or week 96 (mice), and then once every 2 weeks; clinical findings were recorded at 4-week intervals. Water consumption was measured weekly by cage for the first 13 weeks and every 4 weeks thereafter.
Method of Sacrifice	
CO ₂	70%:30% CO ₂ :O ₂

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Pyridine

13-Week Studies	2-Year Studies
<p>Necropsy Necropsy performed on all core study animals. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.</p> <p>Clinical Pathology Blood was collected from the retroorbital sinus of special study rats on days 5 and 20 and of core study rats at the end of the study for hematology and clinical chemistry analyses. Hematology: hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, nucleated erythrocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials Clinical chemistry: urea nitrogen, creatinine, protein, albumin, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbital dehydrogenase, bile acids</p> <p>Histopathology Complete histopathology was performed on 0 and 1,000 ppm F344/N rats, male Wistar rats, and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone (with marrow), brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland (with adjacent skin), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach, testis (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus. The kidney of male rats and the liver of all rats were also examined in all other exposure groups.</p> <p>Sperm Motility and Vaginal Cytology At the end of the studies, sperm samples were collected from male F344/N rats and mice in the 0, 250, 500, and 1,000 ppm groups for sperm motility evaluations. The following parameters were evaluated: spermatid heads per gram testis, spermatid heads per testis, sperm count, epididymal sperm concentration, and epididymal sperm motility. The left cauda, epididymis, and testis were weighed. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies from all females exposed to 0, 250, 500, or 1,000 ppm for vaginal cytology evaluations. The following parameters were evaluated: estrous cycle length and relative frequency of estrous stages.</p> <p>Determinations of Pyridine in Plasma At the end of the 13-week studies, blood was collected from the retroorbital sinus of all rats just before sacrifice for plasma pyridine concentration measurements.</p>	<p>Necropsy performed on all animals.</p> <p>None</p> <p>Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone (with marrow), brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland (with adjacent skin), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach, testis (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus.</p> <p>None</p> <p>None</p>

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes or removed from study for other reasons were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B5, C1, C4, D1, D5, E1, and E5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, D3, and E3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, D3, and E3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account.

More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the k th power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of $k=3$ was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F₁ mice (Portier *et al.*, 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected tests were used in the analysis of lesion incidence, and reported P values are one sided.

Analysis of Continuous Variables Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, plasma concentration, urinalysis, spermatid, and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of

Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunn's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure concentrations.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings

were reviewed and assessed by NTP staff, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of pyridine was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, mutations in L5178Y mouse lymphoma cells, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, sex-linked recessive lethal mutations in *Drosophila melanogaster*, and increases in the frequency of micronucleated erythrocytes in bone marrow of mice. The protocols for these studies and the results are given in Appendix F.

The genetic toxicity studies of pyridine are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the molecular structure and the effects of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemical-induced DNA damage and to predict carcinogenicity in animals, based on the electrophilicity theory of chemical mutagenesis and the somatic mutation theory of cancer (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent

carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone.

The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests appears to be less than the *Salmonella* test (Shelby *et al.*, 1993; Shelby and Witt, 1995). Positive responses in long-term peripheral blood micronucleus tests have not been formally evaluated for their predictivity for rodent carcinogenicity. But, because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical.

RESULTS

F344/N RATS

13-WEEK STUDY

Two females exposed to 1,000 ppm died during week 1; all other F344/N rats survived until the end of the study (Table 2). Final mean body weights of 1,000 ppm males and 500 and 1,000 ppm females and mean body weight gains of males and females exposed to 500 or 1,000 ppm were significantly less than those of the controls. Water consumption by female rats exposed to 1,000 ppm was less than that by the controls. Drinking water concentrations of 50, 100, 250, 500, or 1,000 ppm pyridine resulted in average daily doses of approximately 5, 10, 25, 55, or 90 mg pyridine/kg body weight. There were no exposure-related clinical findings.

TABLE 2
Survival, Body Weights, and Water Consumption of F344/N Rats
in the 13-Week Drinking Water Study of Pyridine

Concentration (ppm)	Survival ^a	Mean Body Weight ^b (g)			Final Weight Relative to Controls (%)	Water Consumption ^c	
		Initial	Final	Change		Week 1	Week 13
Male							
0	10/10	149 ± 4	346 ± 9	197 ± 6		132	78
50	10/10	145 ± 4	345 ± 7	201 ± 5	100	138	76
100	10/10	149 ± 4	348 ± 6	199 ± 5	101	145	74
250	10/10	148 ± 4	346 ± 7	198 ± 4	100	136	82
500	10/10	150 ± 4	328 ± 5	177 ± 2**	95	131	90
1,000	10/10	150 ± 4	296 ± 5**	145 ± 4**	85	128	85
Female							
0	10/10	111 ± 2	206 ± 3	95 ± 2		126	91
50	10/10	110 ± 2	203 ± 4	93 ± 3	99	128	89
100	10/10	110 ± 2	202 ± 2	92 ± 2	98	127	93
250	10/10	111 ± 2	205 ± 4	95 ± 4	100	126	91
500	10/10	108 ± 2	193 ± 1**	85 ± 2*	94	123	98
1,000	8/10 ^d	110 ± 2	187 ± 3**	78 ± 3**	91	85	89

* Significantly different ($P \leq 0.05$) from the control group by Williams' test

** $P \leq 0.01$

^a Number of animals surviving at 13 weeks/number initially in group

^b Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.

^c Water consumption is expressed as grams of water consumed per kg body weight per day.

^d Week of death: 1

The hematology and clinical chemistry data for F344/N rats are listed in Table G1. On day 5, an erythrocytosis, demonstrated by increased hematocrit values, hemoglobin concentrations, and erythrocyte counts relative to controls occurred in males exposed to 100 ppm or greater. An erythrocytosis would be consistent with dehydration, which can cause a relative erythrocytosis due to decreased blood volume and hemoconcentration (Jain, 1986). On day 20, the erythrocytosis was replaced by evidence of a developing normocytic, normochromic, nonresponsive anemia, demonstrated by decreased hematocrit values, hemoglobin concentrations, and erythrocyte counts relative to controls in males and females exposed to 250 ppm or greater. Normocytosis, normochromia, and lack of an erythropoietic response were evidenced by the absence of changes relative to controls in mean cell volumes, mean cell hemoglobin concentrations, and reticulocyte counts, respectively. At week 13, evidence of the anemia persisted in 500 and 1,000 ppm males and expanded to all exposed females.

Albumin and total protein concentrations were increased relative to controls at various time points in males and females exposed to 100 ppm or greater. Increased albumin concentration would be consistent with dehydration and hemoconcentration; overproduction of albumin is not known to occur in any animal (Kaneko, 1989). The increase of total protein is probably a reflection of the increase of albumin. This evidence of dehydration could suggest that the severity of the anemia was tempered by the hemoconcentration and that the anemia may have been more severe than what the data indicate.

There was evidence of hepatocellular injury and/or altered hepatic function demonstrated by increased serum alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentrations that predominantly occurred in 500 and 1,000 ppm males and females relative to controls. Increases of bile acid concentrations also can indicate cholestasis. But activity of serum alkaline phosphatase, another biomarker of cholestasis, was decreased relative to controls in all exposed males and females at various time points; this suggests cholestasis was not involved. However, decreased alkaline phosphatase activity was not exposure concentration-related and, thus, could indicate chemical inhibition of the enzyme or interference with the assay method. Additionally, circulating alkaline phosphatase in a normal rat is primarily of intestinal and bone origin (Righetti and Kaplan, 1971), and fasting or food restriction causes decreases in serum alkaline phosphatase activity (Jenkins and Robinson, 1975). If rats decreased their food intake due to treatment-related toxicity or poor food palatability, decreases in alkaline phosphatase activity relative to controls might be related to loss of the normally circulating intestinal fraction. Thus, increases in alkaline phosphatase activity due to cholestasis could be counterbalanced by the negative effect of decreased food intake. Final mean body weights of 500 and 1,000 ppm males and females were significantly less than those of the controls, supporting the possibility of decreased food intake. Changes in other hematology and clinical chemistry variables were minimal, inconsistent between males and females, and within physiological values; they were not considered toxicologically relevant.

Left epididymis and left testis weights of 1,000 ppm males were significantly less than controls but were probably related to decreased body weights (Table I1). The estrous cycle length of 1,000 ppm females was significantly longer than that of the controls (Table I2).

Absolute and relative liver weights of males exposed to 250, 500, or 1,000 ppm and of females exposed to 100, 250, 500, or 1,000 ppm were significantly greater than controls (Table H1). At the end of the study, plasma concentrations in 50, 100, 250, and 500 ppm females were greater than those in males; however, plasma concentration in 1,000 ppm females was less than males (Table J1).

Multiple hepatic alterations were observed in the livers of males and females exposed to 500 or 1,000 ppm (Table 3). Incidences of centrilobular degeneration and hypertrophy were increased relative to controls in males and females exposed to 500 or 1,000 ppm. Incidences of chronic inflammation were increased in 1,000 ppm males and females and 500 ppm males compared to controls. Incidences of pigmentation were significantly increased in 500 and 1,000 ppm males and females and 250 ppm females relative to controls. Two types of enlarged centrilobular hepatocytes were separately diagnosed. Degeneration consisted of mildly to moderately enlarged, palely stained hepatocytes, primarily centrilobular, that had lacy to vacuolated cytoplasm containing an eosinophilic granular to flocculent material, and hypertrophy was a minimal increase in the size of centrilobular hepatocytes without vacuolated or lacy cytoplasm. Chronic inflammation consisted of lymphocytes, macrophages, and fibrous connective tissue that was primarily centrilobular but bridged across lobules in more severe cases. The macrophages often contained a yellow-brown pigment that special stains showed had characteristics of both lipofuscin and hemosiderin. The pigment was positive with PAS, Perl's, and Schmorl's staining but was acid-fast negative.

TABLE 3
Incidences of Selected Nonneoplastic Lesions in F344/N Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Male						
Liver ^a	10	10	10	10	10	10
Centrilobular, Degeneration ^b	0	0	0	0	9** (1.0) ^c	9** (1.8)
Hypertrophy	0	0	0	0	9** (1.0)	9** (1.0)
Inflammation, Chronic	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	7** (1.0)	9** (1.9)
Pigmentation	0	0	0	0	6** (1.0)	10** (1.1)
Kidney	10	10	10	10	10	10
Casts	0	0	3 (1.0)	3 (1.0)	9** (1.0)	9** (1.0)
Inflammation, Chronic	0	0	0	2 (1.0)	4* (1.0)	9** (1.0)
Mineralization	2 (1.0)	2 (1.0)	2 (1.0)	6 (1.0)	9** (1.0)	10** (1.0)
Renal Tubule, Regeneration	10 (1.0)	10 (1.0)	10 (1.0)	10 (1.1)	10 (1.6)	10 (1.4)
Casts Granular	0	0	0	0	3 (1.0)	8** (1.0)
Renal Tubule, Hyaline Degeneration	1 (1.0)	0	1 (1.0)	1 (1.0)	3 (1.0)	7** (1.0)
Female						
Liver	10	10	10	10	10	10
Centrilobular, Degeneration	0	0	0	0	9** (1.0)	9** (1.8)
Hypertrophy	0	0	0	0	9** (1.0)	8** (1.0)
Inflammation, Chronic	0	0	0	0	1 (1.0)	4* (1.8)
Pigmentation	0	0	0	7** (1.0)	7** (1.0)	8** (1.1)
Kidney	10					10
Casts	0					2 (1.0)
Mineralization	10 (1.6)					10 (1.3)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test

** $P \leq 0.01$

^a Number examined microscopically

^b Number of animals with lesion

^c Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Many of the kidney lesions (protein casts, inflammation, mineralization, and regeneration of renal tubule epithelium) observed in male rats exposed to 500 or 1,000 ppm are components of spontaneous nephropathy that is common in male rats (Table 3). Increased incidences of protein casts, chronic inflammation, and mineralization and the increased severities of renal tubule regeneration in male rats exposed to 500 or 1,000 ppm compared to controls suggest that pyridine exacerbated nephropathy. The incidences of granular casts and renal tubule hyaline degeneration were significantly increased relative to controls in 1,000 ppm males, but the severities were minimal. Granular casts indicate more severe renal tubule damage than protein casts. Hyaline degeneration refers to eosinophilic refractile protein material in

the cytoplasm of the renal tubule epithelium. Immunostaining for α 2u-globulin was positive in males and negative in females.

Exposure Concentration Selection Rationale: A high exposure concentration of 400 ppm was selected for the 2-year F344/N rat study based on increased incidences and severities of liver (including increased alanine aminotransferase and sorbitol dehydrogenase activities and bile acids concentrations) and kidney lesions and a decrease in final mean body weights and body weight gain relative to controls in rats exposed to 500 or 1,000 ppm in the 13-week study. Lesions observed in the liver of female rats exposed to 250 ppm consisted of only scant pigment in macrophages in the vicinity of the central veins, and there was no kidney effect. Toxicokinetic data suggested that 400 to 500 ppm was in a nonlinear portion of the retention curve while 100 and 200 ppm were in the linear range.

2-YEAR STUDY

Survival Estimates of 2-year survival probabilities for male and female F344/N rats are shown in Table 4 and in the Kaplan-Meier survival curves (Figure 2). Survival of exposed males and females was not significantly different from controls.

TABLE 4
Survival of F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	11	13	15	10
Natural deaths	14	17	10	24
Animals surviving to study termination	25	20	25	16
Percent probability of survival at end of study ^a	50	40	50	32
Mean survival (days) ^b	663	666	665	646
Survival analysis ^c	P=0.124	P=0.403	P=1.000	P=0.095
Female				
Animals initially in study	50	50	50	50
Moribund	3	8	7	2
Natural deaths	15	5	14	22
Animals surviving to study termination	32	37	29	26
Percent probability of survival at end of study	64	74	58	52
Mean survival (days)	694	703	693	672
Survival analysis	P=0.055	P=0.392N	P=0.700	P=0.204

^a Kaplan-Meier determinations

^b Mean of all deaths (uncensored, censored, and terminal sacrifice)

^c The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. Lower mortality in an exposure group is indicated by N.

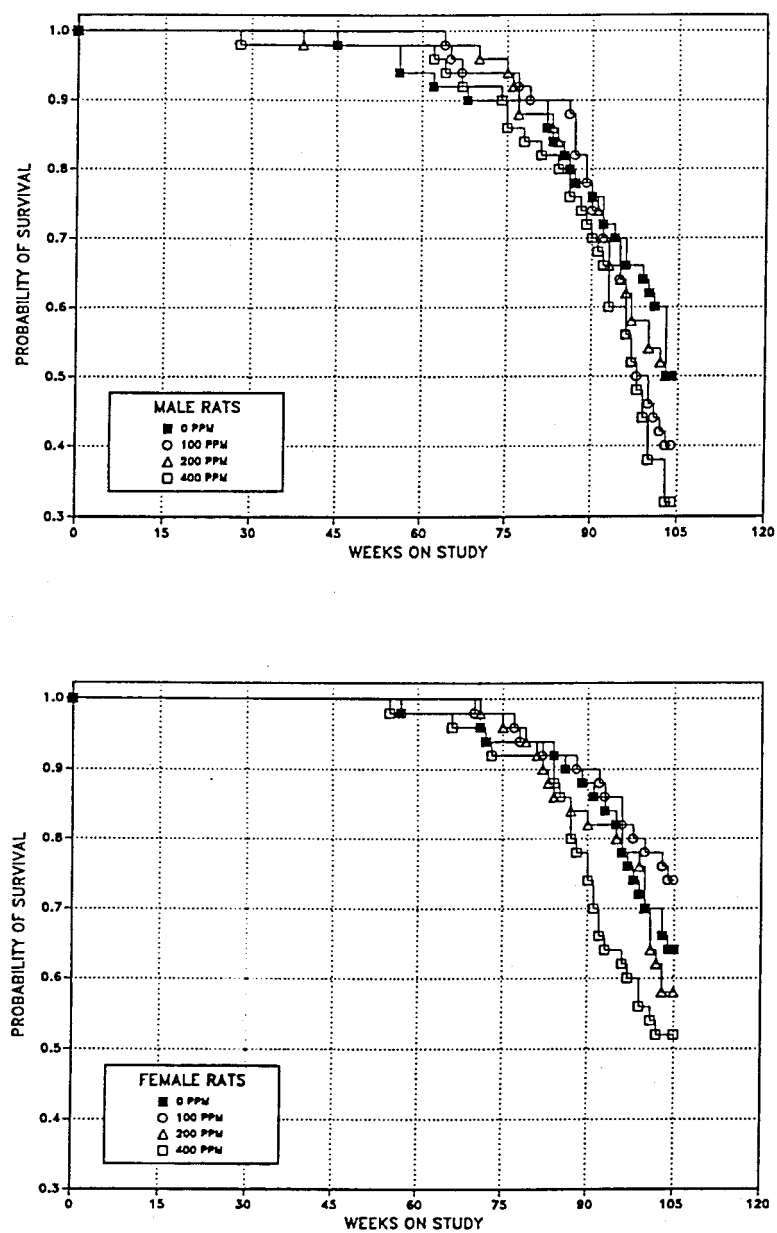


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female F344/N Rats
Exposed to Pyridine in Drinking Water for 2 Years

Body Weights, Water and Compound Consumption, and Clinical Findings Mean body weights of 200 and 400 ppm males after weeks 73 and 6, respectively, and females after weeks 61 and 9, respectively, were less than those of controls (Tables 5 and 6; Figure 3). Water consumption by 400 ppm males and females was greater than that by controls throughout the study, and water consumption by 200 ppm males and females was greater during the second year of the study (Tables L1 and L2). Drinking water concentrations of 100, 200, or 400 ppm pyridine resulted in average daily doses of approximately 7, 14, or 33 mg/kg. There were no treatment-related clinical findings.

TABLE 5
Mean Body Weights and Survival of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

Weeks on Study	0 ppm		100 ppm			200 ppm			400 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	136	50	135	99	50	135	99	50	136	100	50
2	173	50	172	100	50	169	98	50	167	97	50
3	207	50	208	101	50	206	99	50	201	97	50
4	236	50	234	99	50	232	98	50	227	96	50
5	255	50	253	99	50	250	98	50	245	96	50
6	275	50	267	97	50	272	99	50	258	94	50
7	293	50	286	98	50	289	99	50	272	93	50
8	302	50	295	98	50	295	98	50	282	94	50
9	314	50	309	98	50	306	97	50	291	93	50
10	331	50	326	99	50	323	98	50	309	93	50
11	333	50	329	99	50	328	99	50	311	94	50
12	342	50	339	99	50	340	100	50	323	95	50
13	351	50	349	99	50	348	99	50	328	94	50
17	384	50	382	100	50	378	99	50	355	93	50
21	409	50	405	99	50	404	99	50	376	92	50
25	426	50	420	99	50	420	98	50	392	92	50
29	437	50	431	99	50	433	99	50	403	92	49
33	453	50	448	99	50	448	99	50	421	93	49
37	465	50	461	99	50	460	99	50	434	93	49
41	478	50	468	98	50	469	98	49	443	93	49
45	483	50	480	99	50	480	100	49	452	94	49
49	489	49	479	98	50	480	98	49	453	93	49
53	487	49	482	99	50	482	99	49	453	93	49
57	502	47	489	98	50	484	97	49	462	92	49
61	503	47	491	98	50	487	97	49	459	91	49
65	508	46	492	97	49	484	95	49	455	90	47
69	511	45	500	98	47	485	95	49	457	89	46
73	511	45	500	98	47	480	94	48	446	87	46
77	510	45	497	98	47	475	93	46	446	87	43
81	494	45	497	101	45	467	94	44	441	89	42
85	501	42	486	97	45	462	92	41	428	86	40
89	499	39	484	97	41	440	88	39	414	83	37
93	501	36	478	95	35	428	85	35	406	81	33
95	495	35	452	91	35	422	85	33	403	81	30
97	491	33	464	95	28	414	84	30	391	80	28
99	474	33	459	97	25	401	85	29	379	80	24
101	468	31	458	98	23	397	85	27	388	83	19
103	461	29	440	95	21	374	81	26	369	80	19
Mean for weeks											
1-13	273		269	99		269	99		258	95	
14-52	447		442	99		441	99		414	93	
53-103	495		479	97		449	91		425	86	

TABLE 6
Mean Body Weights and Survival of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

Weeks on Study	0 ppm		100 ppm			200 ppm			400 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	110	50	110	100	50	110	101	50	111	101	50
2	129	50	128	99	50	127	99	50	124	96	50
3	144	50	145	100	50	143	99	50	139	96	50
4	152	50	152	100	50	151	99	50	148	97	50
5	160	50	160	100	50	159	100	50	155	97	50
6	167	50	167	100	50	164	98	50	160	96	50
7	173	50	173	100	50	171	98	50	167	96	50
8	180	50	179	100	50	176	98	50	170	95	50
9	183	50	183	100	50	178	97	50	173	94	50
10	186	50	185	100	50	181	98	50	175	94	50
11	192	50	190	99	50	185	96	50	178	93	50
12	196	50	194	99	50	187	96	50	182	93	50
13	198	50	197	100	50	191	97	50	185	93	50
17	213	50	210	99	50	204	96	50	196	92	50
21	223	50	220	99	50	212	95	50	205	92	50
25	228	50	225	99	50	218	95	50	208	91	50
29	234	50	233	100	50	224	96	50	214	91	50
33	242	50	238	98	50	228	94	50	220	91	50
37	251	50	247	98	50	239	95	50	225	90	50
41	261	50	257	99	50	247	95	50	234	90	50
45	270	50	269	100	50	257	95	50	240	89	50
49	279	50	280	101	50	266	95	50	247	89	50
53	285	50	287	101	50	273	96	50	252	88	50
57	288	50	290	101	50	273	95	50	255	89	49
61	299	49	297	99	50	280	94	50	258	86	49
65	301	49	302	100	50	284	94	50	259	86	49
69	310	49	308	99	50	290	93	50	269	87	48
73	314	47	313	100	49	292	93	49	275	88	47
77	322	47	313	97	49	299	93	48	282	88	46
81	326	47	323	99	47	299	92	47	283	87	46
85	330	46	327	99	46	306	93	43	281	85	44
89	331	45	328	99	45	306	92	42	286	86	39
93	338	43	332	98	44	307	91	41	286	85	33
95	334	42	335	100	43	305	91	41	281	84	32
97	344	38	332	96	41	306	89	39	286	83	30
99	340	36	333	98	40	301	89	38	286	84	29
101	337	35	333	99	39	298	89	35	284	85	28
103	340	35	332	98	39	303	89	31	286	84	26
Mean for weeks											
1-13	167		166	99		163	98		159	95	
14-52	245		242	99		233	95		221	90	
53-103	321		318	99		295	92		276	86	

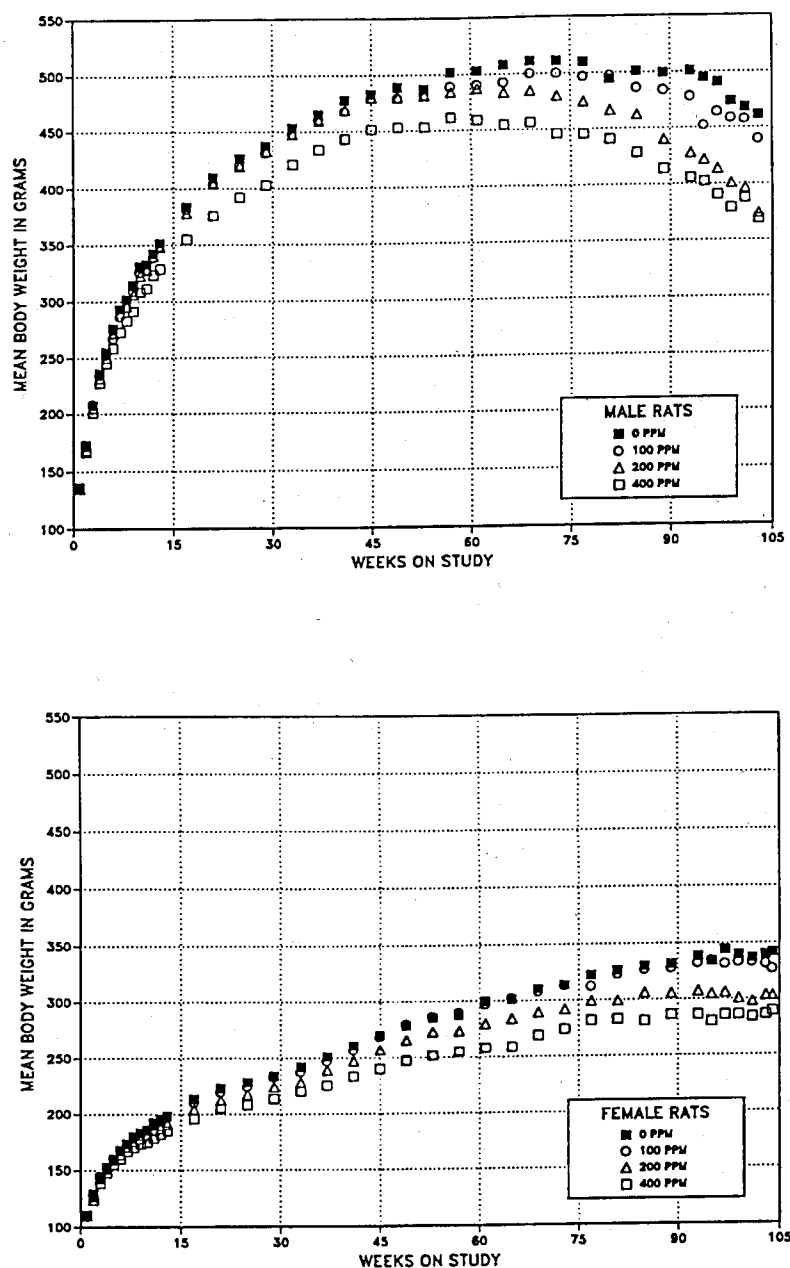


FIGURE 3
Growth Curves for Male and Female F344/N Rats
Exposed to Pyridine in Drinking Water for 2 Years

Pathology and Statistical Analyses This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the kidney, liver, and lung and incidences of mononuclear cell leukemia. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male F344/N rats and Appendix B for female F344/N rats.

Kidney: In the standard evaluation, incidences of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in male rats exposed to 400 ppm were significantly increased compared to controls and exceeded the historical control ranges (Tables 7, A3, and A4). One renal tubule carcinoma was observed in a 100 ppm male. Because of the increased incidence of renal tubule adenoma in 400 ppm males, additional step sections of kidneys were prepared from residual wet tissue so that each kidney yielded four additional sections spaced 1 mm apart. The step sections did not reveal additional carcinomas, but additional adenomas were observed in each group of exposed and control males (Table 7). The incidence of renal tubule hyperplasia was increased in 400 ppm males in single sections compared to controls (Tables 7 and A5).

Renal tubule hyperplasia consisted of multiple layers rather than the normal single layer of epithelium, frequently accompanied by an increased tubule diameter (Plate 1). Severity of hyperplasia depended on the number of layers and the complexity of their patterns. Some had papillary projections, but cells retained their orientation to the basement membrane. The renal tubule adenomas in both single and step sections were typical of those occurring spontaneously. Adenomas were masses of epithelial cells five or more tubule diameters in size (Plate 2). Cells in the adenomas were disorganized and had lost their orientation to the tubule basement membrane. The renal tubule carcinoma observed in the single sections was

TABLE 7
Incidences of Selected Neoplasms and Nonneoplastic Lesions in Male F344/N Rats
in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Kidney	50	48	50	49
Single Sections (Standard Evaluation)				
Nephropathy ^a	47 (2.3) ^b	47 (2.3)	49 (2.5)	49 (2.6)
Renal Tubule, Hyperplasia	1 (1.0)	0	4 (3.0)	7* (1.7)
Renal Tubule, Adenoma ^c (includes multiple)				
Overall rate ^d	1/50 (2%)	0/48 (0%)	2/50 (4%)	6/49 (12%)
Adjusted rate ^e	2.4%	0.0%	4.9%	15.9%
Terminal rate ^f	1/25 (4%)	0/20 (0%)	1/25 (4%)	2/16 (13%)
First incidence (days)	722 (T)	722 (T)	708	644
Poly-3 test ^g	P=0.003	P=0.510N	P=0.498	P=0.042
Renal Tubule, Carcinoma ⁱ	0	1	0	0
Renal Tubule, Adenoma or Carcinoma ^c				
Overall rate	1/50 (2%)	1/48 (2%)	2/50 (4%)	6/49 (12%)
Adjusted rate	2.4%	2.6%	4.9%	15.9%
Terminal rate	1/25 (4%)	1/20 (5%)	1/25 (4%)	2/16 (13%)
First incidence (days)	722 (T)	722 (T)	708	644
Poly-3 test	P=0.008	P=0.750	P=0.498	P=0.042
Step Sections (Extended Evaluation)				
Renal Tubule, Hyperplasia	9 (2.0)	7 (2.1)	11 (3.0)	15 (2.4)
Renal Tubule, Adenoma	1	3	5	9**
Single Sections and Step Sections (Combined)				
Renal Tubule, Hyperplasia	10 (1.9)	7 (2.1)	14 (3.1)	16 (2.4)
Renal Tubule, Adenoma				
Overall rate	2/50 (4%)	3/48 (6%)	6/50 (12%)	10/49 (20%)
Adjusted rate	4.9%	7.6%	14.5%	26.3%
Terminal rate	2/25 (8%)	2/20 (10%)	3/25 (12%)	5/16 (31%)
First incidence (days)	722 (T)	673	627	644
Poly-3 test	P=0.002	P=0.480	P=0.133	P=0.008
Renal Tubule, Carcinoma	0	1	0	0
Renal Tubule, Adenoma or Carcinoma				
Overall rate	2/50 (4%)	4/48 (8%)	6/50 (12%)	10/49 (20%)
Adjusted rate	4.9%	10.2%	14.5%	26.3%
Terminal rate	2/25 (8%)	3/20 (15%)	3/25 (12%)	5/16 (31%)
First incidence (days)	722 (T)	673	627	644
Poly-3 test	P=0.003	P=0.316	P=0.133	P=0.008

TABLE 7
Incidences of Selected Neoplasms and Nonneoplastic Lesions in Male F344/N Rats
in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Stomach, Glandular Mineralization	50 0	49 2 (2.0)	50 2 (1.5)	49 8** (2.0)
Parathyroid Gland Hyperplasia	50 0	50 1 (2.0)	50 3 (2.3)	48 3 (2.0)
Bone Fibrous Osteodystrophy	50 2 (3.0)	50 1 (3.0)	50 4 (2.3)	50 6 (2.5)

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test

** $P \leq 0.01$

(T) Terminal sacrifice

^a Number of animals with lesion

^b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

^c Historical incidence for 2-year drinking water studies with untreated control groups (mean \pm standard deviation): 1/327 (0.3% \pm 0.8%); range, 0%-2%

^d Number of animals with neoplasm per number of animals with kidney examined microscopically

^e Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^f Observed incidence at terminal kill

^g Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposure group is indicated by N.

^h Not applicable; no neoplasms in animal group

ⁱ Historical incidence: 0/327

approximately 3 mm in diameter and had densely packed, widely pleomorphic epithelial cells that infiltrated the adjacent parenchyma.

The severity of nephropathy in males increased slightly with increasing exposure concentration (Table 7).

Incidences of mineralization of the stomach, parathyroid gland hyperplasia, and fibrous osteodystrophy were observed in a few exposed males, and the incidence of stomach mineralization in 400 ppm males was significantly increased compared to controls (Tables 7 and A5). These extrarenal lesions are indicative of kidney disease.

Mononuclear Cell Leukemia: Incidences of mononuclear cell leukemia in female rats were significantly increased in the 200 and 400 ppm groups compared to controls, and the incidence in the 400 ppm group exceeded the historical control range (Tables 8, B3, and B4). In all animals with this neoplasm, neoplastic cells were found in the spleen and usually also in the liver. Infiltrations in the lungs, bone marrow, lymph nodes, adrenal gland, and kidneys were also common. Incidences of mononuclear cell leukemia in male rats were similar to those in controls (0 ppm, 29/50; 100 ppm, 32/50; 200 ppm, 26/50; 400 ppm, 27/50; Table A3).

TABLE 8
Incidences of Mononuclear Cell Leukemia in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Mononuclear Cell Leukemia ^a				
Overall rate ^b	12/50 (24%)	16/50 (32%)	22/50 (44%)	23/50 (46%)
Adjusted rate ^c	26.5%	34.3%	45.4%	48.7%
Terminal rate ^d	8/32 (25%)	12/37 (32%)	8/29 (28%)	5/26 (19%)
First incidence (days)	636	546	496	380
Poly-3 test ^e	P=0.013	P=0.279	P=0.043	P=0.020

^a Historical incidence for 2-year drinking water studies with untreated control groups (mean \pm standard deviation): 102/330 (30.9% \pm 10.0%); range, 16%-44%

^b Number of animals necropsied

^c Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^d Observed incidence at terminal kill

^e Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.

Liver: Incidences of hepatocellular neoplasms were not significantly increased in exposed rats compared to controls, but exposure concentration-related nonneoplastic liver lesions were observed in males and females (Tables 9, A5, and B5). Incidences of centrilobular cytomegaly and cytoplasmic vacuolization were increased in males exposed to 200 or 400 ppm and females exposed to 400 ppm relative to controls. In 400 ppm males, incidences of periportal fibrosis, fibrosis, centrilobular degeneration, and centrilobular necrosis were significantly increased relative to controls. The incidence of centrilobular degeneration was increased in 400 ppm females compared to controls. Bile duct hyperplasia was observed in control and exposed males and females, and the incidences were significantly increased in exposed females compared to controls. Incidences of pigmentation increased compared to controls in all exposed groups of males and in 400 ppm females. Incidences of basophilic focus were decreased relative to controls in 200 and 400 ppm males and all exposed groups of females. The incidence of clear cell focus relative to controls was decreased in 100 ppm males; incidences of clear cell focus were increased relative to controls in 200 and 400 ppm females. The incidence of eosinophilic focus was increased relative to controls in 100 ppm males.

Centrilobular cytomegaly consisted of an increased amount of cytoplasm containing varying amounts of homogeneous eosinophilic material that enlarged hepatocytes. Cytoplasmic vacuolization referred to vacuolized hepatocytes in non-centrilobular areas. Periportal fibrosis consisted of bands of fibrous connective tissue in portal areas. Fibrosis was defined as fibrous connective tissue under the capsule of the liver and extending downward along the vasculature. Bile duct hyperplasia was a cluster of six or more bile ducts. Pigmentation was yellowish brown material in macrophages, often present in areas of fibrosis.

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in F344/N Rats
in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Male				
Number Examined Microscopically	50	49	50	50
Basophilic Focus ^a	12	5	0**	1**
Clear Cell Focus	7	1*	7	4
Eosinophilic Focus	14	23*	23	13
Centrilobular, Cytomegaly	0	4 (1.3) ^b	8** (1.3)	6* (2.0)
Vacuolization Cytoplasmic	4 (1.5)	6 (1.8)	13* (1.7)	17** (2.4)
Periportal Fibrosis	0	0	2 (2.5)	29** (1.8)
Fibrosis	1 (2.0)	1 (2.0)	1 (1.0)	10** (1.6)
Centrilobular, Degeneration	1 (2.0)	3 (2.3)	2 (2.0)	8* (2.1)
Centrilobular, Necrosis	0	3 (1.7)	0	5* (2.2)
Bile Duct, Hyperplasia	46 (1.4)	43 (1.5)	44 (1.6)	49 (1.6)
Pigmentation	4 (1.0)	11* (1.3)	20** (1.3)	25** (2.0)
Hepatocellular Adenoma	1	1	0	3
Hepatocellular Carcinoma	0	0	1	0
Hepatocellular Adenoma or Carcinoma	1	1	1	3
Female				
Number Examined Microscopically	50	50	50	50
Basophilic Focus	38	28*	11**	0**
Clear Cell Focus	4	9	11*	16**
Eosinophilic Focus	19	24	22	15
Centrilobular, Cytomegaly	0	1 (1.0)	4 (1.0)	20** (1.4)
Vacuolization Cytoplasmic	10 (1.8)	7 (1.0)	9 (1.8)	18* (1.6)
Centrilobular, Degeneration	1 (2.0)	2 (2.5)	2 (1.5)	7* (1.1)
Bile Duct, Hyperplasia	20 (1.0)	29* (1.1)	34** (1.0)	29* (1.0)
Pigmentation	6 (1.5)	2 (1.5)	6 (2.3)	17** (1.6)
Hepatocellular Adenoma	1	0	1	0

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test

** $P \leq 0.01$

^a Number of animals with lesion

^b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Lung: Incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in males occurred with a positive trend (1/50, 0/50, 2/50, 4/50; Table A3). Alveolar epithelial hyperplasia was also observed in the 100 and 400 ppm groups (0/50, 3/50, 0/50, 3/50; Table A5). Although these neoplasms are relatively uncommon, incidences up to eight of 50 have occurred in untreated control groups from other recent NTP 2-year carcinogenicity studies. This marginally increased neoplasm incidence was not considered to be chemical related.

WISTAR RATS

13-WEEK STUDY

One male rat exposed to 500 ppm died during the first week of the study (Table 10). Final mean body weights and body weight gains of rats exposed to 250, 500, or 1,000 ppm were significantly less than those of the controls. Water consumption by rats exposed to 1,000 ppm was lower than that by controls. Drinking water concentrations of 50, 100, 250, 500, or 1,000 ppm pyridine resulted in average daily doses of approximately 5, 10, 30, 60, or 100 mg/kg. There were no treatment-related clinical findings.

TABLE 10
Survival, Body Weights, and Water Consumption of Male Wistar Rats
in the 13-Week Drinking Water Study of Pyridine

Concentration (ppm)	Survival ^a	Mean Body Weight ^b (g)			Final Weight Relative to Controls (%)	Water Consumption ^c	
		Initial	Final	Change		Week 1	Week 13
0	10/10	161 ± 3	511 ± 9	350 ± 9		169	120
50	10/10	161 ± 3	476 ± 13	315 ± 11	93	152	118
100	10/10	159 ± 3	490 ± 7	331 ± 8	96	148	116
250	10/10	159 ± 3	463 ± 17**	304 ± 16**	91	136	95
500	9/10 ^d	157 ± 4	443 ± 8**	286 ± 6**	87	141	127
1,000	10/10	159 ± 3	420 ± 15**	260 ± 14**	81	111	74

** Significantly different ($P \leq 0.01$) from the control group by Williams' test

^a Number of animals surviving at 13 weeks/number initially in group

^b Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.

^c Water consumption is expressed as grams of water consumed per kg body weight per day.

^d Week of death: 1

The hematology and clinical chemistry data for Wistar rats are presented in Table G2. Similar to male F344/N rats, an erythrocytosis, demonstrated by increased hematocrit values, hemoglobin concentrations, and erythrocyte counts, occurred in 500 and 1,000 ppm rats on day 5. An erythrocytosis would be consistent with dehydration, which can cause a relative erythrocytosis due to decreased blood volume and hemoconcentration. Hemoconcentration would be supported by the increased albumin concentration in 1,000 ppm rats relative to controls. Additionally, urea nitrogen concentrations were increased relative to controls in 500 and 1,000 ppm rats on days 5 and 20; creatinine concentration, another marker of renal function, was unaffected. Urea nitrogen concentration can be influenced by many extrarenal factors: high

protein diets, dehydration, liver function, animal health, and nutritional status (Finco, 1989). Serum creatinine, a product of muscle metabolism, is not as affected by extrarenal factors (Ragan, 1989). A nonrenal effect, such as dehydration caused by decreased water intake due to poor palatability of dosed water, could result in a urea nitrogen concentration increase, while creatinine concentration remains unchanged.

Also similar to F344/N rats, there was evidence of hepatocellular injury and/or altered hepatic function demonstrated by increased serum alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentrations at all time points in 500 and 1,000 ppm rats relative to controls. Decreased alkaline phosphatase activity relative to controls was observed, but with less consistency, in 250 and 1,000 ppm rats.

Organ weights of exposed rats were not significantly different from those of controls (Table H2). Plasma concentrations of pyridine increased with increasing dose (Table J2).

Incidences of centrilobular degeneration, hypertrophy, chronic inflammation, and pigmentation in the liver of rats exposed to 500 or 1,000 ppm were significantly increased relative to controls (Table 11). Two types of enlarged centrilobular hepatocytes were separately diagnosed. Degeneration consisted of mildly to moderately enlarged, palely stained hepatocytes, primarily centrilobular, that had lacy to vacuolated cytoplasm containing an eosinophilic granular to flocculent material. Hypertrophy was a minimal increase in size of centrilobular hepatocytes without vacuolated or lacy cytoplasm. Chronic inflammation consisted of lymphocytes, macrophages, and fibrous connective tissue that was primarily centrilobular and bridged across lobules in more severe cases. The macrophages often contained a yellow-brown pigment that special stains showed had characteristics of both lipofuscin and hemosiderin. The pigment was positive with PAS, Perl's, and Schmorl's staining but was acid-fast negative.

Incidences of kidney lesions in exposed rats were not significantly different from those of controls (Table 11). Many lesions (protein casts, inflammation, mineralization, and regeneration of renal tubule

epithelium) are components of spontaneous nephropathy that is common in male rats. The incidences of spontaneous nephropathy in control Wistar males were high, and possible nephrotoxicity was not clear. Granular casts, which indicate more severe renal tubule damage than protein casts, were noted in one rat in the 1,000 ppm group. The incidence, but not the severity, of hyaline degeneration was slightly increased in the 1,000 ppm group. Hyaline degeneration refers to eosinophilic refractile protein material in the cytoplasm of renal tubule epithelium. Immunohistochemistry for α 2u-globulin was positive in all rats tested.

TABLE 11
Incidences of Selected Nonneoplastic Lesions in Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Liver ^a	10	10	10	10	9	10
Centrilobular, Degeneration ^b	0	0	0	0	9** (1.7) ^c	9** (1.4)
Hypertrophy	0	0	0	0	9** (1.0)	10** (1.0)
Inflammation, Chronic	0	0	0	2 (1.0)	9** (1.7)	9** (2.2)
Pigmentation	0	0	0	0	9** (1.0)	9** (1.3)
Kidney	10	10	10	10	9	10
Casts	3 (1.0)	3 (1.0)	4 (1.0)	4 (1.5)	4 (1.0)	5 (1.0)
Inflammation, Chronic	0	1 (1.0)	1 (2.0)	0	0	2 (1.0)
Mineralization	7 (1.0)	5 (1.2)	4 (1.0)	8 (1.3)	8 (1.0)	10 (1.0)
Renal Tubule, Regeneration	5 (1.0)	6 (1.0)	5 (1.0)	9 (1.0)	7 (1.0)	8 (1.1)
Casts Granular	0	0	0	0	0	1 (1.0)
Renal Tubule, Hyaline Degeneration	2 (1.0)	0	0	2 (1.0)	3 (1.0)	6 (1.0)

** Significantly different ($P \leq 0.01$) from the control group by the Fisher exact test

^a Number examined microscopically

^b Number of animals with lesion

^c Average severity grade of lesion in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Exposure Concentration Selection Rationale: A high exposure concentration of 400 ppm was selected for the 2-year Wistar rat study based on increased incidences and severities of liver lesions (including increased alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentrations) in rats exposed to 500 or 1,000 ppm compared to controls.

2-YEAR STUDY

Survival Estimates of 2-year survival probabilities for male Wistar rats are shown in Table 12 and in the Kaplan-Meier survival curves (Figure 4). Survival of rats exposed to 200 or 400 ppm was significantly less than that of the controls.

TABLE 12
Survival of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Animals initially in study	50	50	50	50
Moribund	2	9	9	10
Natural deaths	26	27	30	33
Animals surviving to study termination	22	14	11	7
Percent probability of survival at end of study ^a	44	28	22	14
Mean survival (days) ^b	661	625	618	577
Survival analysis ^c	P<0.001	P=0.090	P=0.020	P<0.001

^a Kaplan-Meier determinations

^b Mean of all deaths (uncensored, censored, and terminal sacrifice)

^c The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns.

Body Weights, Water and Compound Consumption, and Clinical Findings Mean body weights of rats exposed to 100, 200, or 400 ppm were significantly less than controls beginning weeks 69, 49, and 6, respectively (Figure 5 and Table 13). Water consumption by exposed rats was similar to that by controls (Table L3). Drinking water concentrations of 100, 200, or 400 ppm pyridine resulted in average daily doses of approximately 8, 17, or 36 mg/kg. There were no treatment-related clinical findings.

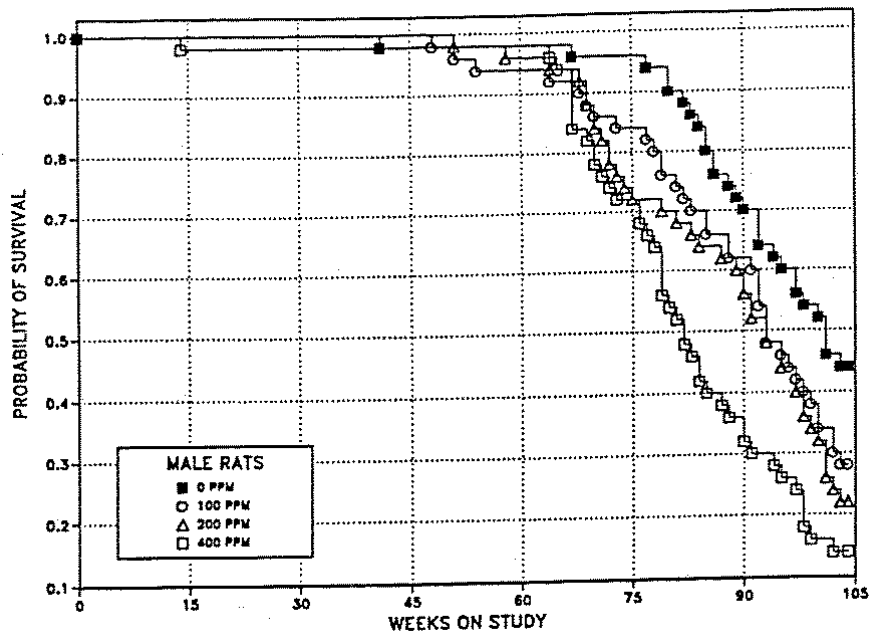


FIGURE 4
Kaplan-Meier Survival Curves for Male Wistar Rats
Exposed to Pyridine in Drinking Water for 2 Years

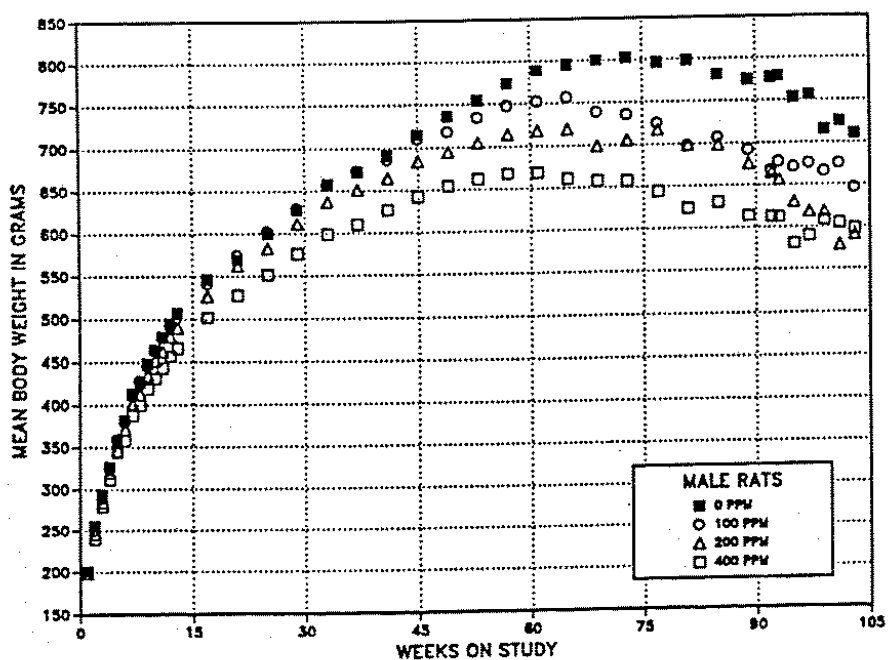


FIGURE 5
Growth Curves for Male Wistar Rats
Exposed to Pyridine in Drinking Water for 2 Years

TABLE 13
Mean Body Weights and Survival of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

Weeks on Study	0 ppm		100 ppm			200 ppm			400 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	201	50	198	98	50	199	99	50	198	98	50
2	255	50	250	98	50	246	97	50	240	94	50
3	294	50	289	98	50	285	97	50	280	95	50
4	327	50	326	100	50	321	98	50	312	95	50
5	357	50	359	101	50	347	97	50	345	96	50
6	382	50	380	99	50	372	97	50	358	94	50
7	413	50	411	100	50	402	97	50	388	94	50
8	426	50	428	101	50	412	97	50	400	94	50
9	448	50	446	100	50	435	97	50	419	94	50
10	464	50	463	100	50	452	97	50	431	93	50
11	479	50	478	100	50	463	97	50	443	93	50
12	494	50	492	100	50	479	97	50	457	93	50
13	506	50	503	99	50	490	97	50	466	92	50
17	546	50	542	99	50	527	97	50	502	92	49
21	569	50	575	101	50	562	99	50	528	93	49
25	599	50	602	101	50	583	97	50	552	92	49
29	627	50	630	100	50	612	98	50	576	92	49
33	658	50	657	100	50	638	97	50	599	91	49
37	672	50	673	100	50	651	97	50	610	91	49
41	691	50	686	99	50	664	96	50	627	91	49
45	715	49	711	99	50	684	96	50	642	90	49
49	736	49	719	98	49	695	94	50	654	89	49
53	755	49	735	97	48	705	93	49	662	88	49
57	774	49	748	97	47	714	92	49	668	86	49
61	789	49	753	95	47	718	91	48	669	85	49
65	795	49	757	95	46	720	91	47	661	83	48
69	800	48	739	92	45	699	87	46	658	82	42
73	803	48	736	92	43	706	88	39	657	82	37
77	797	48	725	91	42	717	90	36	644	81	34
81	799	45	698	87	38	698	88	34	624	78	27
85	782	41	707	91	35	699	89	32	630	81	21
89	775	37	692	89	31	676	87	31	614	79	18
92	777	35	667	86	29	665	86	26	613	79	15
93	779	32	678	87	27	657	84	25	612	79	15
95	753	31	671	89	24	630	84	24	581	77	14
97	757	30	675	89	22	618	82	22	590	78	13
99	715	27	666	93	20	618	86	17	609	85	8
101	725	25	675	93	17	578	80	16	604	83	8
103	710	23	646	91	15	591	83	12	598	84	7
Mean for weeks											
1-13	388		386	99		377	97		364	94	
14-52	646		644	100		624	97		588	91	
53-103	770		704	91		671	87		629	82	

Pathology and Statistical Analyses This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the testis, kidney, and liver. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix C for male Wistar rats.

Testis: The incidence of testicular adenoma in rats exposed to 400 ppm was significantly increased compared to controls (Tables 14 and C3). Interstitial cell hyperplasia was observed in control and exposed groups and the incidences were slightly, but not significantly, increased in rats exposed to 200 or 400 ppm (Tables 14 and C4). The appearance of interstitial cells was similar in both hyperplasia and adenoma and the diagnoses were based on size. Some interstitial cell neoplasms nearly replaced normal tissue (Plate 3). Hyperplasia was defined as a proliferation no larger than the diameter of a seminiferous tubule, and adenoma was larger.

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Testis in Male Wistar Rats
in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Number Examined Microscopically	50	49	49	50
Interstitial Cell Hyperplasia ^a	3 (2.3) ^b	4 (2.0)	7 (2.3)	7 (2.9)
Adenoma				
Overall rate ^c	5/50 (10%)	6/49 (12%)	4/49 (8%)	12/50 (24%)
Adjusted rate ^d	12.3%	16.9%	11.9%	36.6%
Terminal rate ^e	3/22 (14%)	3/14 (21%)	1/11 (9%)	3/7 (43%)
First incidence (days)	592	486	660	464
Poly-3 test ^f	P=0.008	P=0.404	P=0.618N	P=0.012

^a Number examined microscopically

^b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

^c Number of animals with neoplasm per number of animals with testis examined microscopically

^d Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^e Observed incidence at terminal kill

^f Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposure group is indicated by N.

Kidney: Incidences of renal tubule neoplasms in exposed rats were not significantly different from control incidences in the standard evaluation (Tables 15, C1, and C3). Renal tubule adenomas were observed in control and exposed rats and were similar to those observed in F344/N rats. Cells in renal tubule

adenomas were disorganized and had lost their orientation to the tubule basement membrane. One renal tubule carcinoma approximately 5 cm in diameter was observed in the 400 ppm group. This neoplasm had multiple large, solid, irregular proliferations of densely packed, enlarged epithelial cells interspersed with areas of necrosis and inflammatory cells. In an extended evaluation, kidneys were step sectioned because of the carcinoma in the 400 ppm group, because of increased incidences of renal tubule hyperplasia in 100 ppm males relative to controls (Tables 15 and C4), and for comparison with F344/N male rats. Step sections were prepared from residual wet tissue so that each kidney yielded four additional sections spaced 1 mm apart. Step sectioning did not detect any significant treatment-related increase in incidences of renal tubule hyperplasia, adenoma, or carcinoma.

Hyperplasia consisted of multiple layers rather than the normal single layer of cells, frequently accompanied by an increased diameter of the tubule. Severity of hyperplasia depended on the number of layers and the complexity of their patterns. Some had papillary projections, but all maintained their orientation to the basement membrane. Nephropathy was observed in all control and exposed rats (Tables 15 and C4). Nephropathy is a common spontaneous kidney disease that increases in severity with increasing age. Lesions associated with nephropathy include renal cysts, mineralization of basement membranes, and inflammation of the renal parenchyma (Tables 15 and C4). Nephropathy was moderately severe in control and exposed groups of Wistar males and was considered to be the cause of their high mortality in this study. Probably because the kidney lesions were so severe in the controls, no treatment-related increase in the severity of nephropathy could be detected, but incidences of extrarenal lesions of kidney disease such as mineralization in the glandular stomach, parathyroid gland hyperplasia, and fibrous osteodystrophy were generally increased in rats exposed to 100 or 200 ppm compared to controls. Kidney disease in 400 ppm rats may have been less severe because of their lower body weights.

TABLE 15
Incidences of Selected Neoplasms and Nonneoplastic Lesions in Male Wistar Rats
in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
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Kidney ^a	50		50		50		50	
Single Sections (Standard Evaluation)								
Renal Tubule, Hyperplasia ^b	6	(1.7) ^c	17**	(2.1)	8	(2.4)	5	(2.6)
Nephropathy	50	(3.3)	50	(3.6)	50	(3.4)	50	(3.2)
Cyst	21	(2.0)	31	(2.5)	19	(2.5)	16	(2.1)
Mineralization	8	(1.5)	17	(2.1)	8	(1.9)	5	(1.4)
Inflammation, Acute	0		2	(3.0)	0		1	(1.0)
Renal Tubule, Adenoma (includes multiple)	2		5		1		2	
Renal Tubule, Carcinoma	0		0		0		1	
Renal Tubule, Adenoma or Carcinoma	2		5		1		3	
Step Sections (Extended Evaluation)								
Renal Tubule, Hyperplasia	5	(2.2)	13	(2.8)	10	(2.1)	9	(2.8)
Renal Tubule, Oncocytoma	0		1		0		0	
Renal Tubule, Adenoma	1		2		4		2	
Renal Tubule, Carcinoma	0		0		1		0	
Renal Tubule, Adenoma or Carcinoma	1		2		5		2	
Single Sections and Step Sections (Combined)								
Renal Tubule, Hyperplasia	10	(1.8)	22	(2.5)	14	(2.4)	13	(2.8)
Renal Tubule, Adenoma	3		6		5		4	
Renal Tubule, Carcinoma	0		0		1		1	
Renal Tubule, Adenoma or Carcinoma	3		6		6		4	
Stomach, Glandular	49		50		48		48	
Mineralization	8	(2.8)	25**	(2.8)	16*	(2.5)	6	(2.7)
Parathyroid Gland	48		47		48		47	
Hyperplasia	16	(3.3)	32**	(3.2)	29**	(3.0)	12	(2.5)
Bone	50		50		50		50	
Fibrous Osteodystrophy	10	(2.8)	21*	(2.8)	16	(2.9)	6	(1.7)

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test

** $P \leq 0.01$

^a Number examined microscopically

^b Number of animals with lesion

^c Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Liver: Incidences of hepatocellular neoplasms were not increased in exposed Wistar rats compared to controls, but exposure-related nonneoplastic liver lesions were observed (Tables 16, C1, and C4). Incidences of centrilobular degeneration (cytoplasmic vacuolization) occurred in exposed groups and increased with increasing exposure concentration, and the severities of cytoplasmic vacuolization were slightly increased in the exposed groups. The incidence of centrilobular necrosis was increased in the 400 ppm group compared to controls. Incidences of fibrosis and periportal fibrosis were increased in the 200 and 400 ppm groups relative to controls. Incidences of pigmentation were increased in each exposed group compared to controls. The incidences of eosinophilic foci decreased compared to controls in rats exposed to 200 or 400 ppm. In general, these liver lesions were more severe in Wistar rats than in F344/N rats.

The overall structure was maintained, but exposed rats tended to have centrilobular hepatocytes that were necrotic or had an altered appearance and had an increase in fibrous connective tissue in portal areas and extending downward from the liver capsule. Fibrosis was defined as fibrous connective tissue under the capsule of the liver and extending downward along the vasculature. Periportal fibrosis consisted of bands of fibrous connective tissue in portal areas. Pigmentation consisted of yellowish brown material in macrophages.

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Male Wistar Rats
in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Number Examined Microscopically	50	50	50	50
Basophilic Focus ^a	0	0	0	2
Clear Cell Focus	15	7	8	8
Eosinophilic Focus	14	12	4*	2**
Vacuolization Cytoplasmic	18 (1.6) ^b	18 (1.9)	12 (1.8)	15 (1.9)
Centrilobular, Degeneration	1 (1.0)	15** (1.8)	25** (2.1)	33** (2.4)
Centrilobular, Necrosis	5 (2.8)	6 (2.0)	4 (2.8)	23** (2.5)
Fibrosis	1 (2.0)	5 (1.4)	26** (1.6)	31** (1.8)
Periportal Fibrosis	0	0	5* (2.0)	7** (2.4)
Pigmentation	6 (1.5)	15* (1.3)	34** (1.8)	42** (1.8)
Hepatocellular Adenoma	2	0	1	0

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test

** $P \leq 0.01$

^a Number of animals with lesion

^b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

MICE

13-WEEK STUDY

One female mouse exposed to 250 ppm died during week 2 (Table 17). Final mean body weights and body weight gains of female mice exposed to 1,000 ppm were significantly less than those of controls; final mean body weights and body weight gains of all other exposed groups were similar to controls. Water consumption by exposed female mice was lower than that by controls at week 1 but generally slightly higher than controls at week 13; water consumption by exposed and control male mice was similar. Estimated water consumption declined over the course of the study. Drinking water concentrations of 50, 100, 250, 500, or 1,000 ppm pyridine resulted in average daily doses of approximately 10, 20, 50, 85, or 160 mg/kg for males and 10, 20, 60, 100, or 190 mg/kg for females. There were no treatment-related clinical findings.

TABLE 17
Survival, Body Weights, and Water Consumption of Mice
in the 13-Week Drinking Water Study of Pyridine

Concentration (ppm)	Survival ^a	Mean Body Weight ^b (g)			Final Weight Relative to Controls (%)	Water Consumption ^c	
		Initial	Final	Change		Week 1	Week 13
Male							
0	10/10	23.7 ± 0.4	39.4 ± 0.9	15.7 ± 0.8		395	147
50	10/10	23.5 ± 0.3	38.4 ± 1.1	14.9 ± 1.0	97	349	162
100	10/10	23.8 ± 0.3	39.3 ± 0.9	15.4 ± 0.8	100	318	186
250	10/10	23.8 ± 0.3	40.2 ± 1.1	16.3 ± 1.0	102	364	167
500	10/10	23.4 ± 0.3	39.1 ± 0.8	15.8 ± 0.6	99	336	146
1,000	10/10	23.7 ± 0.3	37.2 ± 0.7	13.5 ± 0.6	94	377	121
Female							
0	10/10	19.0 ± 0.3	33.6 ± 1.1	14.6 ± 1.0		441	149
50	10/10	18.7 ± 0.3	37.4 ± 1.1	18.8 ± 1.1	111	278	147
100	10/10	18.9 ± 0.1	34.4 ± 0.9	15.5 ± 0.8	102	271	192
250	9/10 ^d	18.7 ± 0.3	34.2 ± 1.1	15.4 ± 1.0	102	375	214
500	10/10	19.4 ± 0.3	33.2 ± 0.9	13.8 ± 0.8	99	292	172
1,000	10/10	18.7 ± 0.2	29.7 ± 0.9**	11.0 ± 0.8**	88	201	195

** Significantly different ($P \leq 0.01$) from the control group by Williams or Dunnett's test

^a Number of animals surviving at 13 weeks/number initially in group

^b Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.

^c Water consumption is expressed as grams of water consumed per kg body weight per day.

^d Week of death: 2

Sperm motility in exposed male mice was decreased relative to controls (Table I3). There were no significant differences in estrous cycle lengths between control and exposed females (Table I4).

Absolute and relative liver weights were significantly increased relative to controls in males exposed to 100 ppm or greater and in 250 and 500 ppm females (Table H3). No histopathologic lesions were observed in the liver despite increased liver weights in both male and female mice compared to controls, nor were any chemical-related lesions observed in any other tissue.

Exposure Concentration Selection Rationale: The high exposure concentration for the 2-year male mouse study was set at 1,000 ppm based on the lack of target organ lesions in the 13-week study. The high exposure concentration for the 2-year female mouse study was set at 500 ppm based on decreased mean body weight gains relative to controls and decreased water consumption.

2-YEAR STUDY

Survival Estimates of 2-year survival probabilities for male and female mice are shown in Table 18 and in the Kaplan-Meier survival curves (Figure 6). Survival of exposed males and females was similar to that of the controls.

TABLE 18
Survival of Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Male				
Animals initially in study	50	50	50	50
Accidental deaths ^a	2	1	1	3
Other ^a	0	0	1	0
Moribund	2	3	3	1
Natural deaths	11	18	11	11
Animals surviving to study termination	35	28	34	35
Percent probability of survival at end of study ^b	73	57	71	75
Mean survival (days) ^c	685	660	670	656
Survival analysis ^d	P=0.507N	P=0.138	P=0.928	P=1.000N
	0 ppm	125 ppm	250 ppm	500 ppm
Female				
Animals initially in study	50	50	50	50
Accidental deaths ^a	3	6	4	5
Moribund	3	2	3	5
Natural deaths	12	12	21	11
Animals surviving to study termination	32	30	22	29
Percent probability of survival at end of study	68	68	48	65
Mean survival (days)	671	640	638	624
Survival analysis	P=0.487	P=1.000N	P=0.090	P=0.755

^a Censored from survival analyses

^b Kaplan-Meier determinations

^c Mean of all deaths (uncensored, censored, and terminal sacrifice)

^d The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A negative trend or lower mortality in an exposure group is indicated by N.

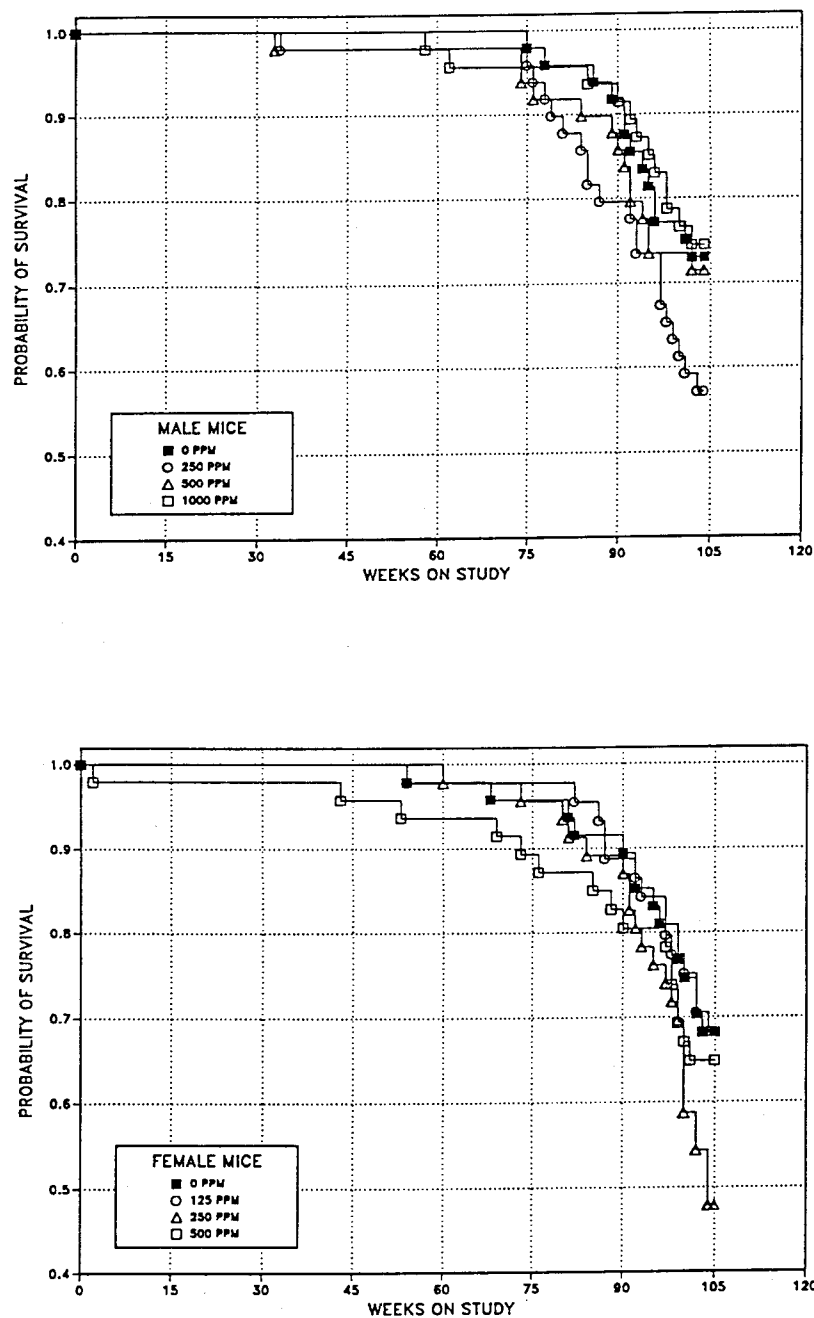


FIGURE 6
Kaplan-Meier Survival Curves for Male and Female Mice
Exposed to Pyridine in Drinking Water for 2 Years

Body Weights, Water and Compound Consumption, and Clinical Findings Mean body weights of exposed males were similar to those of the controls; mean body weights of 500 and 1,000 ppm females were less than controls from weeks 89 and 73, respectively (Tables 19 and 20; Figure 7). Water consumption by males exposed to 250 or 500 ppm was generally greater than that by controls during the last year of the study; male mice exposed to 1,000 ppm consumed less water than controls throughout the study (Table L4). Water consumption by exposed females was generally lower than that by controls during the first year of the study, but greater than controls during the second year (Table L5). Drinking water concentrations of 250, 500, or 1,000 ppm pyridine resulted in average daily doses of approximately 35, 65, or 110 mg/kg for male mice and concentrations of 125, 250, or 500 ppm pyridine resulted in average daily doses of approximately 15, 35, or 70 mg/kg for female mice. There were no treatment-related clinical findings.

TABLE 19
Mean Body Weights and Survival of Male Mice in the 2-Year Drinking Water Study of Pyridine

Weeks on Study	0 ppm		250 ppm			500 ppm			1,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	26.1	50	25.9	99	50	25.8	99	50	25.8	99	50
2	27.6	50	27.4	99	49	27.3	99	49	26.6	96	49
3	29.2	50	28.7	98	49	29.0	99	49	28.4	97	48
4	30.9	50	30.5	99	49	30.7	99	49	30.1	97	48
5	32.8	50	32.3	99	49	32.2	98	49	30.6	93	48
6	33.9	50	34.2	101	49	33.5	99	49	32.0	94	48
7	35.4	50	35.4	100	49	35.3	100	49	33.9	96	48
8	37.6	50	37.1	99	49	36.7	98	49	35.6	95	48
9	38.7	50	37.9	98	49	37.7	97	49	36.5	94	48
10	39.6	50	40.1	101	49	39.8	101	49	37.7	95	47
11	40.6	50	41.0	101	49	41.0	101	49	38.8	96	47
12	41.8	50	42.3	101	49	41.7	100	49	39.8	95	47
13	42.4	50	42.9	101	49	42.7	101	49	40.6	96	47
17	47.0	50	46.2	98	49	45.9	98	49	43.5	93	47
21	48.1	49	48.3	100	49	47.4	99	49	45.2	94	47
25	50.0	49	49.6	99	49	49.9	100	49	47.5	95	47
29	49.6	49	50.8	102	49	51.3	103	49	48.5	98	47
33	51.6	49	51.7	100	49	51.1	99	49	50.0	97	47
37	53.2	49	52.9	99	48	53.0	100	48	51.8	97	47
41	54.5	49	53.8	99	48	53.7	99	48	52.5	96	47
45	54.1	49	53.9	100	48	54.4	101	48	52.7	97	47
49	55.3	49	54.6	99	48	55.4	100	48	53.4	97	47
53	55.4	49	55.6	100	48	56.2	101	48	54.7	99	47
57	55.2	49	55.4	100	48	56.0	101	48	54.0	98	47
61	55.2	49	56.1	102	48	56.4	102	48	54.2	98	46
65	54.4	49	56.3	104	48	56.1	103	48	54.1	99	45
69	55.1	49	56.5	103	48	55.5	101	48	54.4	99	45
73	54.4	49	56.6	104	48	53.9	99	48	54.1	99	45
77	52.8	48	55.1	104	46	52.2	99	45	52.4	99	45
81	51.4	47	53.7	105	44	50.2	98	45	49.2	96	45
85	49.2	46	51.5	105	42	47.8	97	44	47.3	96	45
89	46.6	45	49.7	107	39	45.8	98	44	45.6	98	44
93	45.5	41	46.4	102	37	44.7	98	39	43.7	96	42
97	43.8	37	43.6	100	36	42.9	98	36	41.8	95	39
99	44.5	37	43.5	98	32	42.7	96	36	41.2	93	37
101	44.2	37	41.9	95	30	41.6	94	36	40.6	92	36
103	44.0	35	41.2	94	28	40.0	91	35	39.8	91	35
Mean for weeks											
1-13	35.1		35.1	100		34.9	99		33.6	96	
14-52	51.5		51.3	100		51.3	100		49.5	96	
53-103	50.1		50.9	102		49.5	99		48.5	97	

TABLE 20
Mean Body Weights and Survival of Female Mice in the 2-Year Drinking Water Study of Pyridine

Weeks on Study	0 ppm		125 ppm			250 ppm			500 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	20.8	50	20.7	100	50	20.6	99	50	20.5	99	50
2	21.8	50	21.4	98	49	21.6	99	49	21.5	99	50
3	23.2	50	22.8	98	49	22.8	98	49	22.6	97	47
4	24.1	50	24.0	100	47	23.9	99	49	23.7	98	47
5	25.5	50	25.3	99	47	25.5	100	49	25.6	100	47
6	26.7	50	26.5	99	47	26.3	99	48	26.9	101	47
7	28.2	50	28.4	101	47	28.8	102	47	28.5	101	47
8	29.6	50	29.9	101	47	29.8	101	47	30.0	101	47
9	31.1	50	30.1	97	47	30.8	99	47	30.4	98	47
10	31.7	49	32.0	101	47	32.7	103	47	32.9	104	47
11	33.3	49	33.2	100	47	33.7	101	47	33.7	101	47
12	34.1	49	34.2	100	47	35.2	103	47	35.1	103	47
13	35.8	49	35.5	99	47	36.5	102	47	36.3	101	47
17	40.2	49	39.4	98	47	40.5	101	47	40.4	101	47
21	41.1	49	40.0	97	47	41.6	101	47	41.4	101	47
25	45.9	48	44.2	96	47	45.8	100	47	45.1	98	47
29	45.7	48	44.9	98	46	47.2	103	46	46.5	102	46
33	49.1	48	47.7	97	46	49.5	101	46	48.7	99	46
37	51.0	48	49.4	97	46	51.0	100	46	50.1	98	46
41	53.1	48	51.1	96	46	53.2	100	46	52.0	98	46
45	54.0	48	52.5	97	46	54.1	100	46	52.2	97	45
49	56.2	48	54.5	97	46	55.6	99	46	54.4	97	45
53	56.9	48	55.6	98	46	57.1	100	46	55.5	98	45
57	58.2	47	56.4	97	45	58.0	100	46	56.8	98	44
61	59.5	47	57.9	97	44	59.3	100	45	58.1	98	44
65	59.9	47	58.5	98	44	61.0	102	45	58.6	98	43
69	61.6	46	59.3	96	44	62.1	101	45	58.2	95	43
73	62.8	46	60.2	96	44	62.2	99	45	58.0	92	42
77	63.3	46	61.0	96	44	61.9	98	44	55.4	88	40
81	62.2	45	60.3	97	43	60.4	97	43	51.6	83	40
85	61.1	43	58.6	96	42	58.8	96	41	48.7	80	39
89	60.0	43	58.0	97	39	54.4	91	41	45.8	76	37
93	57.4	40	56.3	98	38	50.9	89	37	43.7	76	36
97	55.7	38	52.7	95	37	47.1	85	35	40.2	72	36
99	56.1	37	53.3	95	34	46.1	82	33	40.1	72	33
101	55.5	35	52.5	95	33	42.8	77	27	39.9	72	30
103	56.1	33	50.7	90	31	41.2	73	25	39.1	70	29
Mean for weeks											
1-13	28.1		28.0	100		28.3	101		28.3	101	
14-52	48.5		47.1	97		48.7	100		47.9	99	
53-103	59.1		56.8	96		54.9	93		50.0	85	

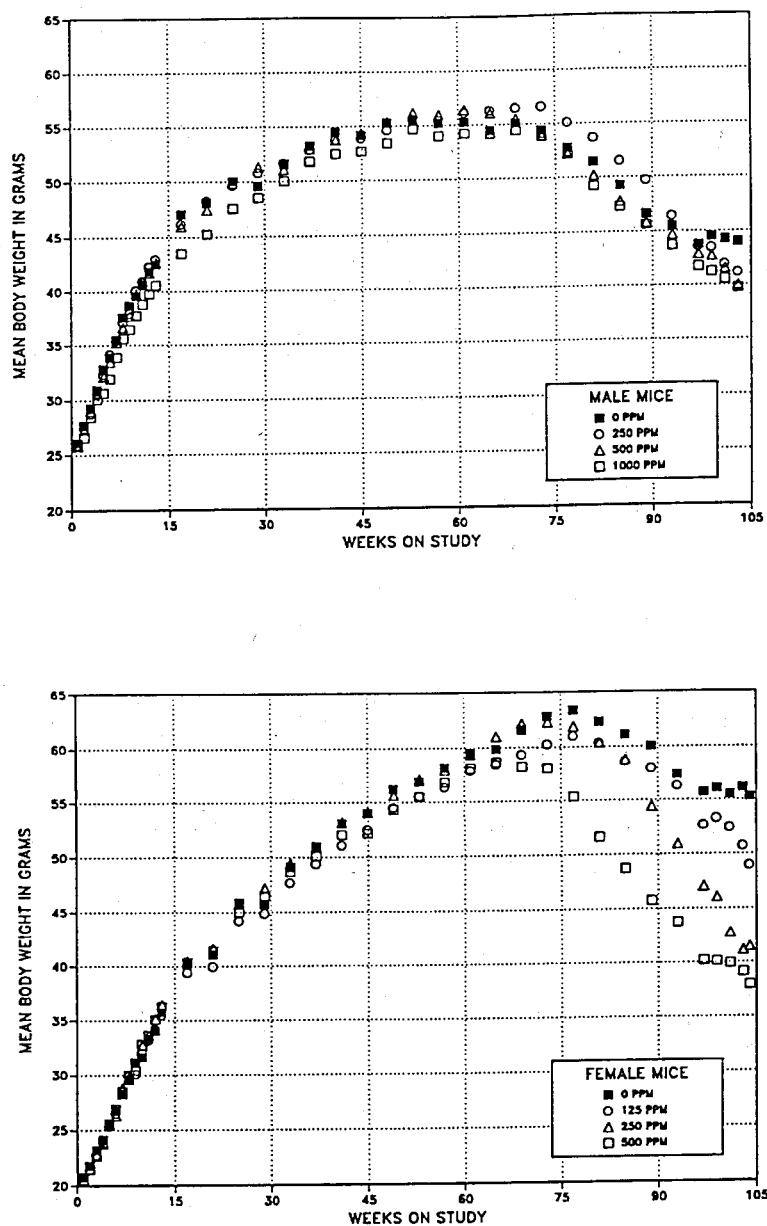


FIGURE 7
Growth Curves for Male and Female Mice
Exposed to Pyridine in Drinking Water for 2 Years

Pathology and Statistical Analyses This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the liver and other organs. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix D for male mice and Appendix E for female mice.

Liver: Hepatocellular neoplasms in male and female mice were clearly related to pyridine exposure. Incidences of hepatocellular adenoma were significantly increased relative to controls in 250 ppm males and females and 1,000 ppm males (Tables 21, D3, and E3). Incidences of hepatocellular carcinoma and hepatoblastoma were significantly increased relative to controls in all exposed groups of males and females except for the incidence of hepatoblastoma in 125 ppm females. Incidences of hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined) were significantly increased in all exposed male groups and in 250 and 500 ppm females relative to controls. The incidences of hepatocellular neoplasms in exposed males and females generally exceeded the historical control ranges (Tables 21, D4, and E4). Incidences of hepatoblastoma in control and exposed males and females exceeded the historical control range.

TABLE 21
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice
in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Male				
Number Examined Microscopically	50	50	49	50
Basophilic Focus ^a	3	1	0	0
Eosinophilic Focus	19	22	18	15
Mixed Cell Focus	4	2	1	1
Hepatocellular Adenoma, Multiple				
Overall rate ^b	16/50 (32%)	29/50 (58%)*	29/49 (59%)*	28/50 (56%)*
Hepatocellular Adenoma (includes multiple) ^c				
Overall rate	29/50 (58%)	40/50 (80%)	34/49 (69%)	39/50 (78%)
Adjusted rate ^d	63.2%	88.0%	75.7%	84.9%
Terminal rate ^e	24/35 (69%)	27/28 (96%)	27/34 (79%)	31/35 (89%)
First incidence (days)	520	522	513	406
Poly-3 test ^f	P=0.031	P=0.003	P=0.134	P=0.011
Hepatocellular Carcinoma, Multiple				
Overall rate	3/50 (6%)	19/50 (38%)**	26/49 (53%)**	18/50 (36%)**
Hepatocellular Carcinoma (includes multiple) ^g				
Overall rate	15/50 (30%)	35/50 (70%)	41/49 (84%)	40/50 (80%)
Adjusted rate	32.3%	78.7%	89.9%	85.1%
Terminal rate	9/35 (26%)	23/28 (82%)	32/34 (94%)	28/35 (80%)
First incidence (days)	574	522	513	406
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
Hepatoblastoma, Multiple				
Overall rate	1/50 (2%)	4/50 (8%)	6/49 (12%)*	2/50 (4%)
Hepatoblastoma (includes multiple) ^h				
Overall rate	2/50 (4%)	18/50 (36%)	22/49 (45%)	15/50 (30%)
Adjusted rate	4.5%	41.2%	49.8%	34.4%
Terminal rate	2/35 (6%)	11/28 (39%)	17/34 (50%)	13/35 (37%)
First incidence (days)	722 (T)	549	514	624
Poly-3 test	P=0.005	P<0.001	P<0.001	P<0.001
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma ⁱ				
Overall rate	38/50 (76%)	47/50 (94%)	46/49 (94%)	47/50 (94%)
Adjusted rate	80.1%	98.9%	98.5%	100.0%
Terminal rate	29/35 (83%)	28/28 (100%)	34/34 (100%)	35/35 (100%)
First incidence (days)	520	522	513	406
Poly-3 test	P<0.001	P=0.002	P=0.003	P<0.001

TABLE 21
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice
in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Female				
Number Examined Microscopically	49	50	50	50
Basophilic Focus	1	0	0	0
Eosinophilic Focus	17	12	14	9
Mixed Cell Focus	5	4	3	0
Hepatocellular Adenoma, Multiple				
Overall rate	24/49 (49%)	34/50 (68%)*	37/50 (74%)**	30/50 (60%)
Hepatocellular Adenoma (includes multiple) ^j				
Overall rate	37/49 (76%)	39/50 (78%)	43/50 (86%)	34/50 (68%)
Adjusted rate	82.5%	87.9%	97.3%	79.1%
Terminal rate	27/32 (84%)	27/30 (90%)	22/22 (100%)	23/29 (79%)
First incidence (days)	554	419	509	430
Poly-3 test	P=0.372N	P=0.336	P=0.015	P=0.442N
Hepatocellular Carcinoma, Multiple				
Overall rate	3/49 (6%)	11/50 (22%)*	14/50 (28%)**	30/50 (60%)**
Hepatocellular Carcinoma (includes multiple) ^k				
Overall rate	13/49 (27%)	23/50 (46%)	33/50 (66%)	41/50 (82%)
Adjusted rate	29.8%	55.0%	78.1%	97.1%
Terminal rate	8/32 (25%)	18/30 (60%)	20/22 (91%)	29/29 (100%)
First incidence (days)	476	573	556	479
Poly-3 test	P<0.001	P=0.014	P<0.001	P<0.001
Hepatoblastoma, Multiple				
Overall rate	0/49 (0%)	0/50 (0%)	3/50 (6%)	4/50 (8%)
Hepatoblastoma (includes multiple) ^l				
Overall rate	1/49 (2%)	2/50 (4%)	9/50 (18%)	16/50 (32%)
Adjusted rate	2.4%	4.9%	21.6%	39.6%
Terminal rate	1/32 (3%)	1/30 (3%)	3/22 (14%)	12/29 (41%)
First incidence (days)	729 (T)	599	564	510
Poly-3 test	P<0.001	P=0.493	P=0.007	P<0.001
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma ^m				
Overall rate	41/49 (84%)	42/50 (84%)	45/50 (90%)	44/50 (88%)
Adjusted rate	89.9%	94.6%	99.6%	99.5%
Terminal rate	29/32 (91%)	29/30 (97%)	22/22 (100%)	29/29 (100%)
First incidence (days)	476	419	509	430
Poly-3 test	P=0.009	P=0.323	P=0.042	P=0.045

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test

** $P \leq 0.01$

^a Number of animals with lesion

^b Number of animals with neoplasm per number of animals with liver examined microscopically

^c Historical incidence for 2-year drinking water studies with untreated control groups (mean \pm standard deviation): 179/289 (61.9% \pm 9.1%); range, 47%-70%

^d Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^e Observed incidence at terminal kill

^f Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposure group is indicated by N.

^g Historical incidence: 80/289 (27.7% \pm 11.7%); range, 10%-42%

^h Historical incidence: 9/289 (3.1% \pm 5.0%); range, 0%-12%

ⁱ Historical incidence: 212/289 (73.4% \pm 11.7%); range, 53%-81%

^j Historical incidence: 150/289 (51.9% \pm 20.8%); range, 26%-80%

^k Historical incidence: 55/289 (19.0% \pm 13.7%); range, 8%-42%

^l Historical incidence: 0/289

^m Historical incidence: 173/289 (59.9% \pm 21.3%); range, 32%-82%

Many mice had multiple hepatocellular neoplasms. Hepatocellular neoplasms in exposed mice were similar

to those that occur spontaneously. A hepatocellular adenoma was typically a discrete proliferation of

hepatocytes that compressed adjacent tissue and had uneven growth patterns resulting in a slightly abnormal architecture (Plate 4). Hepatocellular carcinomas had a distinctly altered structure, cells were often pleomorphic, and the boundary with the adjacent parenchyma was often unclear (Plate 5). Hepatoblastomas had very poorly differentiated (frequently basophilic, small, and spindloid) cells that had a markedly altered architecture of solid sheets, rosettes, ribbons, or trabeculae (Plate 6). Hepatoblastomas nearly always were found in the midst of a hepatocellular carcinoma, but unless there was a clearly separate hepatocellular carcinoma, only the diagnosis of hepatoblastoma was made.

Some of the hepatocellular carcinomas and many of the hepatoblastomas had areas of necrosis, and metastatic lesions were noted in the lungs or, less frequently, in the lymph nodes or adjacent abdominal organs (Tables D5 and E5). There were no treatment-related increased incidences of foci of cellular alteration relative to controls (Tables 21, D5, and E5). Foci of cellular alteration were contiguous hepatocytes of less than a lobule up to approximately four lobules that varied tinctorially from the rest of the liver but which tended to merge imperceptibly with the adjacent parenchyma.

Liver neoplasms from control mice, 500 ppm females, and 1,000 ppm males were stained for p53 protein and compared to a control carcinoma from the mammary gland of a p53 positive transgenic mouse. All of the liver sections tested were negative for p53 protein.

Other Organs: Incidences of hematopoietic cell proliferation in the spleen were increased in exposed males (0 ppm, 13/49; 250 ppm, 30/50; 500 ppm, 26/47; 1,000 ppm, 23/49; Table D5) and females (0 ppm, 29/49; 125 ppm, 27/50; 250 ppm, 32/48; 500 ppm, 39/49; Table E5) relative to controls and may have been compensation for destruction of blood cells in the altered vasculature of the hepatic neoplasms and their metastases. Increased incidences of follicular cell hyperplasia in the thyroid gland of exposed males and females were not accompanied by a significant increased incidence of thyroid gland neoplasms relative to controls (males: 8/49, 14/50, 20/49, 12/50; females: 14/50, 21/50, 22/50, 23/50; Tables D1, D5, E1, and E5). An apparent decrease in the incidences of hyaline degeneration in the respiratory epithelium of exposed males and females (males: 20/50, 10/49, 15/49, 15/50; females: 26/50, 16/50,

12/47, 13/50) and increases in incidences of hyaline degeneration in the olfactory epithelium of exposed females (19/50, 27/50, 35/47, 36/50) compared to controls were of unknown biological significance.

Hyaline degeneration in the nasal epithelium is an accumulation of eosinophilic material in the cytoplasm and a common alteration in aging mice.

GENETIC TOXICOLOGY

Pyridine (100-10,000 $\mu\text{g}/\text{plate}$) was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9 metabolic activation enzymes (Haworth *et al.*, 1983; Table F1). Further, no significant increase in mutant frequencies was observed in L5178Y mouse lymphoma cells, tested with and without S9 metabolic activation (McGregor *et al.*, 1988; Table F2). In cytogenetic tests with cultured Chinese hamster ovary cells, pyridine did not induce sister chromatid exchanges (Table F3) or chromosomal aberrations (Table F4), with or without S9. At the highest viable dose (1,673 $\mu\text{g}/\text{mL}$) tested for sister chromatid exchange induction in the absence of S9, pyridine induced marked cell cycle delay, and an extended culture time (31 hours) was used to allow sufficient cells to accumulate for analysis.

Pyridine was tested on three separate occasions in two different laboratories for induction of sex-linked recessive lethal mutations in adult male *Drosophila melanogaster* (Valencia *et al.*, 1985; Mason *et al.*, 1992; Table F5), and mixed results were obtained. In the first experiment (Valencia *et al.*, 1985), administration of pyridine by injection (7,000 ppm in aqueous 0.7% saline solution) gave negative ($P=0.225$) results, but feeding (700 ppm pyridine in aqueous 5% sucrose) produced an increase in recessive lethal mutations that was considered to be equivocal ($P=0.043$). A second experiment performed in the same laboratory using both injection (500 ppm) and feeding (729 ppm) yielded negative results. In the third experiment (Mason *et al.*, 1992) performed in a second laboratory, results of a feeding (500 ppm) experiment were negative ($P=0.998$), but administration of pyridine by injection (4,300 ppm) induced a significant increase in the frequency of sex-linked recessive lethal mutations ($P=0.008$). This positive

result in the sex-linked recessive lethal test led to the performance of a test for induction of reciprocal translocations in germ cells of treated male *Drosophila melanogaster* (Mason *et al.*, 1992; Table F6); results of this test were negative.

In vivo assays for chromosomal effects were conducted with male mice. No induction of chromosomal aberrations (Table F7) was noted in bone marrow cells at either of two sampling times (400-600 mg/kg pyridine; single injection), and no increase in the frequency of micronucleated polychromatic erythrocytes (Table F8) was noted in bone marrow after intraperitoneal injection of pyridine (up to 500 mg/kg administered three times at 24-hour intervals).

In summary, with the exception of the single positive result obtained in a *Drosophila melanogaster* sex-linked recessive lethal assay, no indication of mutagenic activity was seen with pyridine in a variety of *in vitro* and *in vivo* assays for gene mutation and chromosomal damage.

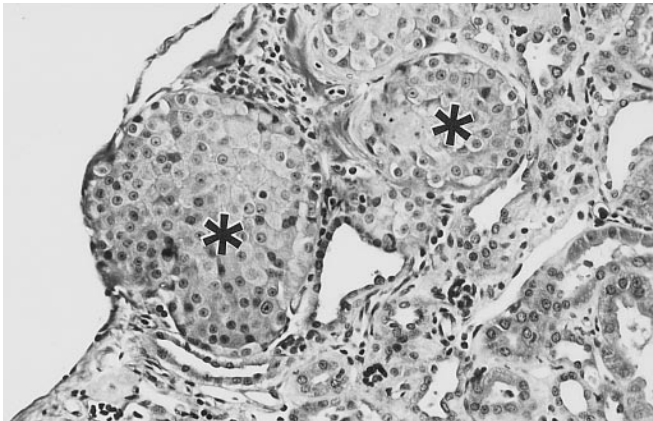


PLATE 1

Kidney from a male F344 rat given exposed to 400 ppm pyridine in drinking water for 2 years. Hyperplasia of the renal tubular epithelium are indicated by asterisks. Note that multiple cross sections of the tubule are distended with epithelial cells. H&E; 66 ×

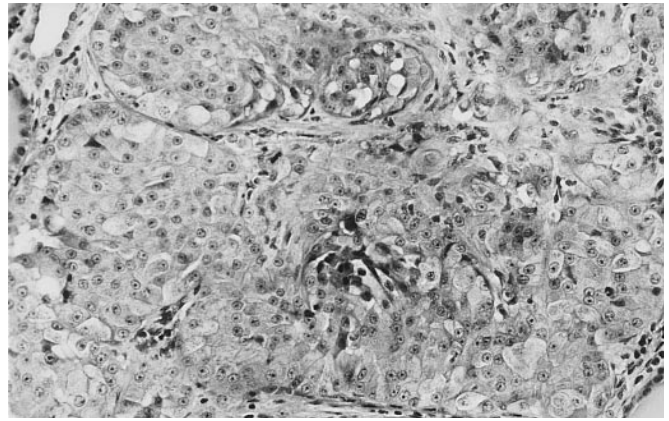


PLATE 2

Kidney from a male F344 rat exposed to 400 ppm pyridine in drinking water for 2 years. Note the renal tubule adenoma consisting of a larger cluster of cells than a hyperplasia and resulting in a loss of tubular structure. H&E; 66 ×



PLATE 3

Testis from a male Wistar rat exposed to 400 ppm pyridine in drinking water for 2 years. A large interstitial cell adenoma compresses degenerate seminiferous tubules (arrows). H&E; 13 ×

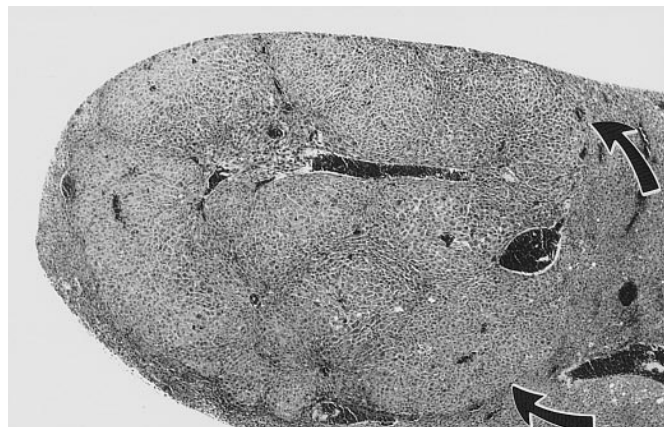


PLATE 4

Liver from a female B6C3F1 mouse exposed to 250 ppm pyridine in the drinking water for 2 years. A large hepatocellular adenoma compresses (arrow) the parenchyma. H&E; 8 ×

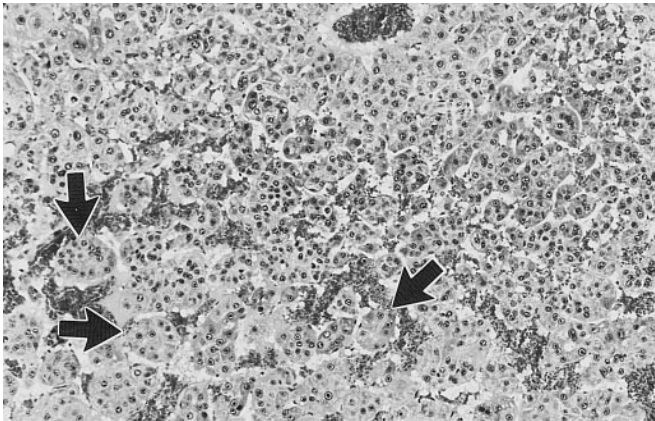


PLATE 5

Liver from a male B6C3F1 mouse exposed to 1,000 ppm pyridine for 2 years. A hepatocellular carcinoma with a trabecular pattern shows clusters of hepatocytes (arrows) rather than the normal lobular architecture. H&E; 33 ×

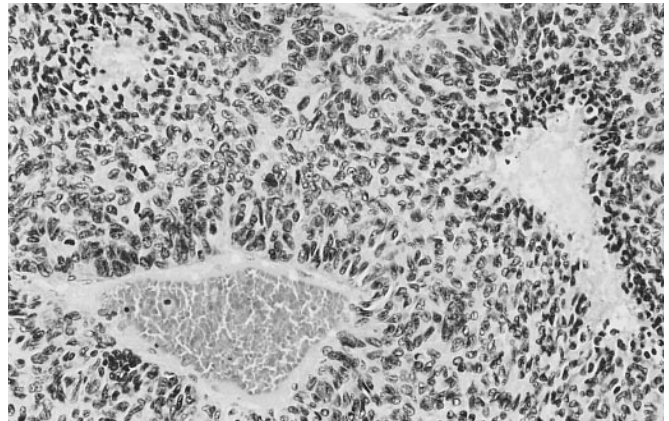


PLATE 6

Liver from a male B6C3F1 mouse exposed to 500 ppm pyridine for 2 years. Note the small spindle-shaped cells of a hepatoblastoma rather than normal polyhedral hepatocytes. H&E; 66 ×

DISCUSSION AND CONCLUSIONS

Pyridine was nominated by the National Cancer Institute for toxicity and carcinogenicity studies because of its large annual production and the potential for human exposure. No previous 2-year carcinogenesis bioassays for pyridine have been reported in the literature. Pyridine is used in a variety of industrial processes including the production of pesticides and herbicides, and it is found as a natural component in some foods.

Based on water consumption in the 13-week studies, the estimated dose of pyridine delivered to animals exposed to 50, 100, 250, 500, or 1,000 ppm pyridine was 5, 10, 25, 55, or 90 mg pyridine/kg body weight for male and female F344/N rats; 5, 10, 30, 60, or 100 mg/kg for male Wistar rats; 10, 20, 50, 85, or 160 mg/kg for male mice; and 10, 20, 60, 100, or 190 mg/kg for female mice.

The target organs in the 13-week rat studies included the liver and kidney in male F344/N and Wistar rats and the liver in female F344/N rats. The liver lesions consisted of centrilobular degeneration, hypertrophy, chronic inflammation, and pigmentation at 500 and 1,000 ppm. The liver lesions in male Wistar rats were similar to those in F344/N rats. Kidney lesions in male rats included renal tubule regeneration and hyaline degeneration, protein casts, chronic inflammation, and/or mineralization. These lesions are components of chronic nephropathy, a spontaneous condition in rats that usually increases in severity with age.

In the 13-week study, incidences of refractile eosinophilic protein material (hyaline degeneration) in the renal tubule epithelium were increased relative to controls in 1,000 ppm male F344/N rats but were of the same minimal severity. These protein droplets typically contain a low-molecular weight protein, α_2u , that is synthesized in the liver under the control of androgens. The α_2u protein is normally filtered in the glomerulus; approximately half is reabsorbed by proximal tubule epithelium, and half is excreted in the

urine (Neuhaus *et al.*, 1981). Normally only small amounts of the reabsorbed α 2u protein are visible as hyaline droplets because it is soon degraded by enzymes in the tubule epithelium. Some chemicals (inducers) combine with reabsorbed α 2u and make it more resistant to enzymatic degradation, resulting in protein material accumulation in the renal tubule epithelium (Lehman-McKeeman *et al.*, 1989).

In this study, although there appeared to be increased incidences of hyaline protein droplets in the renal tubule epithelium of male F344/N and Wistar rats, the minimal severities of this finding in control and exposed males suggested that pyridine did not cause a retention of α 2u protein. Immunohistochemistry for α 2u demonstrated its presence in all male F344/N and Wistar rats, both control and exposed, in the 13-week studies.

The liver and kidney have previously been reported as target organs in rats administered pyridine in feed at 0.34% to 1.0% for up to 4 months (Baxter, 1948). Liver toxicity was observed in Sprague-Dawley rats administered pyridine at 50 mg/kg per day by oral gavage for 13 weeks (Anderson, 1987). Thus, the target organs in the current studies were similar to what has previously been reported. Decreased water consumption and/or body weight effects were observed in 1,000 ppm mice relative to controls in the 13-week study, but no target organ lesions were observed.

Based on water consumption in the 2-year studies, the estimated dose of pyridine delivered to rats exposed to 100, 200, or 400 ppm in drinking water was 7, 14, or 33 mg/kg for male and female F344/N rats and 8, 17, or 36 mg/kg for male Wistar rats.

In the 2-year rat studies, there was a subtle increase in the severities of nephropathy in 200 and 400 ppm male F344/N rats. Nephropathy in 100 and 200 ppm male Wistar rats was more severe than in F344/N rats and was accompanied by incidences of extrarenal lesions associated with kidney disease. Incidences of dilated renal tubules, in particular, were more frequent in Wistar rats than in F344/N rats. A slight increase relative to controls in incidences of renal tubule hyperplasia in 400 ppm male F344/N rats and 100 ppm Wistar rats was also observed. The extrarenal lesions were not as significantly increased in 400

ppm Wistar rats as in the 100 and 200 ppm groups. The low survival rate and decreased mean body weights of 400 ppm Wistar rats may have decreased their chance for developing kidney disease.

In 400 ppm male F344/N rats, there was a marginal increase in the incidence of renal tubule adenoma relative to controls. The NTP has found that examination of the entire kidney by step sectioning may enable a more precise evaluation of the potential chemical-related induction of renal proliferative lesions than observations made from single sections, particularly when the proliferative lesions are small and identified only by microscopic examination (Eustis *et al.*, 1994). For pyridine, this extended evaluation showed an exposure concentration-related increase in the incidence of renal tubule adenoma, which was significantly increased relative to controls in 400 ppm male F344/N rats; this was considered some evidence for a carcinogenic effect. The subtle increase in the severities of nephropathy observed in exposed male F344/N rats may have influenced the induction, development, or progression of renal neoplasms in several ways, including a reduction in target cell population and/or increased numbers of cells in the replicative cycle due to chronic inflammation and continued degeneration and necrosis, alterations in vascularity as a result of fibrosis, or other alterations in the microenvironment that might have contributed to the development of cancer at this site.

Kidney changes consistent with a marginally increased severity of nephropathy were observed in both the 13-week and 2-year rat studies. With certain chemicals, binding to α 2u-globulin has been associated with male rat renal tubule neoplasms and exacerbated nephropathy (USEPA, 1991), but in these studies of pyridine, this phenomenon did not appear to account for the renal tubule neoplasms. Both control and exposed male rats stained positive for α 2u-globulin in the 13-week studies, as was indicated earlier, but retention of this material in the kidneys of exposed rats was inconsequential, and α 2u-globulin formation was not considered to be involved in the kidney neoplasm formation.

There was no evidence for a carcinogenic effect in the kidney of Wistar rats. The same diagnostic criteria and terminology were used in evaluating lesions in the kidney of both strains of rats. The severity of spontaneous nephropathy in control Wistar rats was moderate, whereas that in control male F344/N rats

was mild. The results of these studies suggest that the male Wistar rat is not as susceptible as the male F344/N rat to the formation of kidney neoplasms from pyridine exposure. The NTP has not compared the susceptibility of male F344/N rats and male Wistar rats to other kidney carcinogens.

In the Wistar rat at 2 years, the incidence of interstitial cell adenomas of the testis was increased in the 400 ppm group relative to controls. There was no corresponding increase in interstitial cell hyperplasia. The NTP does not have a historical database for neoplasms in Wistar rats. In one study analyzing neoplasm rates in 1,370 control Wistar rats (from Charles River, Kingston, NY, or Hilltop Laboratory Animals, Scottsdale, PA, and studied from 1980 to 1990) a control rate of 3.9% (range, 0%-22%) was reported for interstitial cell neoplasms of the testis in animals weighing between 556 and 717 g (Walsh and Poteracki, 1994). The rate for interstitial cell adenomas in the 400 ppm pyridine Wistar rat was only marginally outside this historical range, and incidences of this neoplasm were not increased relative to controls in the 100 or 200 ppm groups. This was considered to be equivocal evidence for a carcinogenic effect. The mean body weights of the control male Wistar rats in this study were somewhat higher during the second year of the study (reaching a high of 803 g at week 73). Increased body weights have been associated with higher neoplasm rates at some sites in rodents, and this difference, combined with other differences in animal husbandry condition and time of study, may be a factor in the incidences of interstitial cell neoplasms observed in the present study. The spontaneous rate for interstitial cell neoplasms of the testis in F344/N rats is high (about 90%) and often precludes the detection of a carcinogenic effect at this site.

Mononuclear cell leukemia is a common neoplasm in F344/N rats. The Wistar rat was added to these studies because it has a low background incidence of mononuclear cell leukemia in comparison to the male F344/N rat, and there was concern from a previous study by Dieter *et al.* (1989) that pyridine may cause leukemia. However, in these studies, pyridine did not appear to affect the rate for leukemia in male rats. Incidences of mononuclear cell leukemia were increased in 200 and 400 ppm F344/N female rats relative to controls and were considered to be equivocal evidence of carcinogenic activity rather than some evidence of carcinogenic activity because the increase was at or just outside the historical control range for

this neoplasm (range, 16%-44%) and there was no supportive evidence for an increase in mononuclear cell leukemia in male rats. Relative to incidences of mononuclear cell leukemia in control animals in a concurrent drinking water study at the same laboratory (19/50; NTP, 1997a), the rate of 23/50 observed in the 400 ppm group in this study does not seem to be significant.

Liver lesions in F344/N rats were characterized by centrilobular cytomegaly, degeneration, and necrosis; cytoplasmic vacuolization; foci of cellular alteration; fibrosis; and pigmentation in Kupffer s cells and macrophages. Bile duct hyperplasia was observed in all exposed groups of males and females and the incidences were significantly increased in exposed females compared to controls. Periportal fibrosis was a prominent lesion in 400 ppm males. There were no statistically significant increases in the incidences of hepatocellular neoplasms in exposed F344/N or Wistar rats.

The same diagnostic criteria and terminology were applied to the liver lesions in both strains of rats. In general, except for the incidences of centrilobular cytomegaly, which was highest in 400 ppm females, periportal fibrosis, which was highest in 400 ppm male F344/N rats, and cytoplasmic vacuolization, which occurred in control and exposed Wistar rats, treatment-related nonneoplastic liver lesions occurred at higher incidences and with greater severities in Wistar rats than in male or female F344/N rats. These lesions, along with nephropathy, probably contributed to early deaths in Wistar rats. Incidences of fibrosis, extending from the liver capsule downwards into the parenchyma, were significantly increased relative to controls in 200 and 400 ppm Wistar rats but were increased less significantly in 400 ppm male F344/N rats and were not treatment related in females.

Based on water consumption in the 2-year study, the estimated doses of pyridine delivered to male mice exposed to 250, 500, or 1,000 ppm were 35, 65, or 110 mg/kg, and for female mice exposed to 125, 250, or 500 ppm, were 15, 35, or 70 mg/kg.

Exposure to pyridine was associated with progression of liver neoplasms from benign to malignant in male and female mice. Hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas represent a

biological and morphological continuum in progression of proliferative lesions. It is probable that hepatoblastomas do not represent further progression to a more malignant state but rather are composed of cells that are more primitive. Hepatoblastomas are considered to represent a phenotypic, and possibly genotypic, variant of a malignant liver neoplasm. Because the malignant potential of hepatocellular carcinomas and hepatoblastomas appear similar and hepatoblastomas are generally observed in the hepatocellular neoplasms (mostly carcinomas), it is appropriate to combine the incidences of hepatoblastomas with those of hepatocellular adenoma and carcinoma when interpreting the carcinogenic potential of a chemical. Hepatoblastomas, which are rare, are observed in relatively high numbers only after chemical administration (primarily in mice) and have previously been observed in NTP studies with primidone (NTP, 1997b), oxazepam (NTP, 1993a), *o*-nitroanisole (NTP, 1993b), benzofuran (NTP, 1989), ethylene thiourea (NTP, 1992), 1-amino-2,4-dibromoanthraquinone (NTP, 1996), methylphenidate hydrochloride (NTP, 1995), and coumarin (NTP, 1993c).

Liver cancer accounts for approximately 2% to 3% of all cancer deaths in the United States (Parker *et al.*, 1996). In children, hepatoblastomas account for approximately 70% of the liver cancers (Ding *et al.*, 1994).

Pyridine is metabolized primarily by N-methylation and/or aromatic hydroxylation. Metabolites identified include N-methylpyridinium, 3-hydroxy pyridine, and N-methyl pyridinium hydroxide. Pyridine is metabolized by cytochromes P2E1 and P4B (CYP2E1 and CYP4B) (Nikula *et al.*, 1995) and enhances the expression of several forms of P₄₅₀, including CYP2E1, CYP1A1/1A2, and CYP2B1/2B2 in both hepatic and renal tissues (tissues from rat used as the model system) (Kim and Novak, 1990; Kim *et al.*, 1991a; Kim *et al.*, 1993). Pyridine, like primidone (NTP, 1997b), phenobarbital (McClain, 1990), and oxazepam (NTP, 1993a, 1997c), induces liver neoplasms in mice but not in rats, even though in rats these chemicals cause a spectrum of toxic liver lesions. The mouse, an animal with a high background rate of liver neoplasms, seems to be particularly sensitive to subsequent development of malignant neoplasms after chemical exposure (Drinkwater *et al.*, 1990; Drinkwater, 1994; Bennett *et al.*, 1995; Lee *et al.*, 1995). While there are no studies of the relationship between pyridine exposure and cancer incidence, it is of

interest that use of primidone and phenobarbital to treat epilepsy in humans has not been associated with liver cancer in humans (NTP, 1997b). Some studies suggest that the induction of cytochrome P₄₅₀2B enzymes are associated with mouse liver neoplasm formation (Lubet *et al.*, 1989; Rice *et al.*, 1994). Pyridine-induced liver neoplasms from control, 500 ppm male, and 1,000 ppm female mice showed no accumulation of p53 antibody, a marker that correlates with p53 gene alterations. Another nonmutagenic mouse liver carcinogen, methylphenidate, also showed no evidence for p53 protein accumulation in methylphenidate-induced liver neoplasms in the B6C3F₁ mouse and was negative in the p53 (+/-) transgenic mouse model (Tennant *et al.*, 1995).

Pyridine is negative in most studies for genotoxicity. Pyridine was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9 metabolic activation enzymes. Further, no significant increase in mutant frequencies was observed in L5178Y mouse lymphoma cells, tested with and without S9 metabolic activation. In cytogenetic tests with cultured Chinese hamster ovary cells, pyridine did not induce sister chromatid exchanges or chromosomal aberrations, with or without S9. Results were positive for the induction of sex-linked recessive lethal mutations in *Drosophila melanogaster* following injection of pyridine but were negative by the same route of administration for induction of reciprocal translocations in germ cells of *D. melanogaster*. No induction of chromosomal aberrations and no increase in the frequency of micronucleated polychromatic erythrocytes was noted in mouse bone marrow cells after intraperitoneal injection of pyridine.

There is a developing field of study regarding specific genetic changes in mouse and human liver neoplasms. In one series of human hepatoblastomas, p53 alterations were not seen in hepatoblastomas of fetal or mesenchymal origin but did occur in hepatoblastomas classified as small cell (Ruck *et al.*, 1994). Other studies also report a low frequency of p53 mutations in hepatoblastomas (Kar *et al.*, 1993; Kennedy *et al.*, 1994). In contrast, in a study of hepatoblastomas in Japanese patients, p53 mutations were found in nine of 10 cases (Oda *et al.*, 1995). Overexpression of p53 is a rare event in Caucasian patients with hepatocellular carcinoma (Laurent-Puig *et al.*, 1992). Accumulation of p53 protein has been associated with liver neoplasms caused by viral hepatitis (42%) (Ojanguren *et al.*, 1995; Greenblatt *et al.*, 1997) and

in aflatoxin hepatocarcinogenesis (Shen and Ong, 1996). Three studies of liver neoplasms in mice suggest that the p53 gene plays a minimal role in the development of these neoplasms (Kress *et al.*, 1992; Chen *et al.*, 1993; Calvert *et al.*, 1995). Mutations of the neoplasm suppressor gene p53 have been found in hepatocellular carcinomas from patients in many countries (e.g., Japan and Asian countries) where there may be an association between neoplasms and virus infection or aflatoxin exposure. In the United States, p53 mutations are usually not found in hepatocellular carcinomas (Kazachkov *et al.*, 1996), and the etiology of the liver cancer is not known.

CONCLUSIONS

Under the conditions of these 2-year drinking water studies, there was *some evidence of carcinogenic activity** of pyridine in male F344/N rats based on increased incidences of renal tubule neoplasms. There was *equivocal evidence of carcinogenic activity* of pyridine in female F344/N rats based on increased incidences of mononuclear cell leukemia. There was *equivocal evidence of carcinogenic activity* in male Wistar rats based on an increased incidence of interstitial cell adenoma of the testis. There was *clear evidence of carcinogenic activity* of pyridine in male and female B6C3F₁ mice based on increased incidences of malignant hepatocellular neoplasms.

In F344/N rats, exposure to pyridine resulted in increased incidences of centrilobular cytomegaly and degeneration, cytoplasmic vacuolization, and pigmentation in the liver of males and females; periportal fibrosis, fibrosis, and centrilobular necrosis in the liver of males; and bile duct hyperplasia in females. In male Wistar rats, pyridine exposure resulted in increased incidences of centrilobular degeneration and necrosis, fibrosis, periportal fibrosis, and pigmentation in the liver, and secondary to kidney disease, mineralization in the glandular stomach and parathyroid gland hyperplasia.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 16.

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APPENDIX A **SUMMARY OF LESIONS IN MALE F344/N RATS** **IN THE 2-YEAR DRINKING WATER STUDY** **OF PYRIDINE**

TABLE A1	Summary of the Incidence of Neoplasms in Male F344/N Rats	
	in the 2-Year Drinking Water Study of Pyridine	A-3
TABLE A2	Individual Animal Tumor Pathology of Male F344/N Rats	
	in the 2-Year Drinking Water Study of Pyridine	A-6
TABLE A3	Statistical Analysis of Primary Neoplasms in Male F344/N Rats	
	in the 2-Year Drinking Water Study of Pyridine	A-22
TABLE A4	Historical Incidence of Renal Tubule Neoplasms in Untreated Male F344/N Rats	A-26
TABLE A5	Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats	
	in the 2-Year Drinking Water Study of Pyridine	A-27

TABLE A1
Summary of the Incidence of Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine^a

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	13	15	10
Natural deaths	14	17	10	24
Survivors				
Terminal sacrifice	25	20	25	16
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(48)	(50)	(49)
Lipoma			1 (2%)	
Intestine large, cecum	(49)	(47)	(50)	(49)
Lipoma			1 (2%)	
Intestine small, duodenum	(50)	(47)	(50)	(48)
Intestine small, jejunum	(50)	(47)	(50)	(47)
Carcinoma	1 (2%)			
Intestine small, ileum	(50)	(47)	(50)	(47)
Liver	(50)	(49)	(50)	(50)
Cholangiocarcinoma				1 (2%)
Hepatocellular carcinoma			1 (2%)	
Hepatocellular adenoma	1 (2%)	1 (2%)		2 (4%)
Hepatocellular adenoma, multiple				1 (2%)
Histiocytic sarcoma	1 (2%)			
Mesentery	(11)	(14)	(7)	(8)
Schwannoma benign	1 (9%)			
Oral mucosa	(1)		(2)	
Pharyngeal, squamous cell papilloma	1 (100%)		1 (50%)	
Pancreas	(50)	(48)	(50)	(49)
Acinus, adenoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(49)	(50)	(49)
Squamous cell papilloma			1 (2%)	
Stomach, glandular	(50)	(49)	(50)	(49)
Tongue				(1)
Squamous cell papilloma				1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Carcinoma		1 (2%)		
Adrenal medulla	(50)	(49)	(50)	(49)
Pheochromocytoma complex				1 (2%)
Pheochromocytoma benign	11 (22%)	2 (4%)	14 (28%)	4 (8%)
Bilateral, pheochromocytoma benign	6 (12%)	1 (2%)		
Islets, pancreatic	(50)	(48)	(50)	(49)
Adenoma	4 (8%)	2 (4%)	1 (2%)	
Parathyroid gland	(50)	(50)	(50)	(48)

TABLE A1
Summary of the Incidence of Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Endocrine System (continued)				
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	16 (32%)	13 (26%)	12 (24%)	11 (22%)
Pars intermedia, adenoma	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(49)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	2 (4%)		3 (6%)	2 (4%)
C-cell, carcinoma		1 (2%)		
Follicular cell, adenoma		2 (4%)		
General Body System				
None				
Genital System				
Epididymis	(49)	(49)	(49)	(48)
Preputial gland	(50)	(47)	(49)	(48)
Adenoma	3 (6%)		7 (14%)	2 (4%)
Carcinoma	5 (10%)	2 (4%)		1 (2%)
Prostate	(50)	(48)	(50)	(49)
Seminal vesicle	(50)	(47)	(50)	(48)
Testes	(49)	(49)	(49)	(48)
Bilateral, interstitial cell, adenoma	33 (67%)	35 (71%)	37 (76%)	40 (83%)
Interstitial cell, adenoma	9 (18%)	8 (16%)	6 (12%)	3 (6%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Melanoma malignant, metastatic, skin			1 (2%)	
Lymph node	(20)	(25)	(20)	(23)
Lymph node, mandibular	(50)	(50)	(50)	(50)
Lymph node, mesenteric	(50)	(47)	(50)	(48)
Spleen	(49)	(48)	(50)	(49)
Thymus	(50)	(49)	(48)	(50)
Thymoma benign				1 (2%)
Integumentary System				
Mammary gland	(49)	(48)	(50)	(49)
Carcinoma		1 (2%)		
Fibroadenoma	4 (8%)	3 (6%)	6 (12%)	4 (8%)
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma				1 (2%)
Keratoacanthoma	6 (12%)	4 (8%)	1 (2%)	5 (10%)
Keratoacanthoma, multiple			1 (2%)	
Squamous cell papilloma	4 (8%)	1 (2%)	1 (2%)	
Trichoepithelioma		1 (2%)		1 (2%)
Pinna, melanoma malignant			1 (2%)	2 (4%)
Subcutaneous tissue, fibroma	4 (8%)	2 (4%)	4 (8%)	
Subcutaneous tissue, lipoma	1 (2%)		1 (2%)	
Musculoskeletal System				
Skeletal muscle		(1)		

TABLE A1
Summary of the Incidence of Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Nervous System				
Brain	(50)	(50)	(48)	(50)
Oligodendroglioma malignant		1 (2%)		
Spinal cord	(1)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			4 (8%)
Alveolar/bronchiolar carcinoma			2 (4%)	
Carcinoma, metastatic, mammary gland		1 (2%)		
Carcinoma, metastatic, Zymbal's gland		1 (2%)		
Melanoma malignant, metastatic, skin			1 (2%)	
Osteosarcoma, metastatic, nose	1 (2%)			
Nose	(50)	(50)	(49)	(50)
Osteosarcoma	1 (2%)			
Respiratory epithelium, squamous cell carcinoma		1 (2%)		
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
Zymbal's gland	(1)	(1)	(1)	(1)
Carcinoma	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Urinary System				
Kidney	(50)	(48)	(50)	(49)
Mesenchymal tumor malignant		1 (2%)		
Renal tubule, adenoma	1 (2%)		1 (2%)	4 (8%)
Renal tubule, adenoma, multiple			1 (2%)	2 (4%)
Renal tubule, carcinoma		1 (2%)		
Urinary bladder	(50)	(47)	(50)	(49)
Systemic Lesions				
Multiple organs ^b	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Leukemia mononuclear	29 (58%)	32 (64%)	26 (52%)	27 (54%)
Lymphoma malignant				1 (2%)
Mesothelioma benign	1 (2%)		1 (2%)	
Mesothelioma malignant	1 (2%)	1 (2%)		
Neoplasm Summary				
Total animals with primary neoplasms ^c	49	49	49	49
Total primary neoplasms	151	120	133	123
Total animals with benign neoplasms	47	46	48	49
Total benign neoplasms	112	77	102	89
Total animals with malignant neoplasms	34	40	29	29
Total malignant neoplasms	39	43	31	34
Total animals with metastatic neoplasms	1	2	1	
Total metastatic neoplasms	1	2	2	

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	3	3	3	4	4	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7
	0	8	8	3	7	7	7	7	9	0	0	2	4	4	5	6	6	9	9	0	1	1	1	1	1
	9	8	8	4	3	1	4	9	5	2	4	5	0	4	6	7	7	2	5	1	5	8	8	9	9
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	1	3	4	2	4	4	1	1	1	0	3	0	3	4	1	4	0	0	2	4	0	1	0	1
	5	2	4	5	3	1	8	5	1	0	7	6	4	8	3	9	4	2	1	2	9	5	6	3	3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Histiocytic sarcoma																									
Mesentery					+	+	+				+								+					+	+
Schwannoma benign																									X
Oral mucosa											+														
Pharyngeal, squamous cell papilloma											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign							X													X	X		X		
Bilateral, pheochromocytoma benign																		X					X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X						X				X			
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X		X		X					X					X	X		X				
Pars intermedia, adenoma												X													
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Penis																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Carcinoma				X																					

+: Tissue examined microscopically
A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7			
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total		
	0	0	0	1	1	1	2	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	Tissues/ Tumors		
	6	8	9	4	7	8	0	1	4	6	7	8	9	0	1	2	3	5	7	9	0	2	6	7	0	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Carcinoma																								1		
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Hepatocellular adenoma																								1		
Histiocytic sarcoma																					X			1		
Mesentery	+		+						+														+	11		
Schwannoma benign																								1		
Oral mucosa																								1		
Pharyngeal, squamous cell papilloma																								1		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Acinus, adenoma										X										X				2		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Tooth					+			+																2		
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Pheochromocytoma benign						X				X				X				X		X	X	X		11		
Bilateral, pheochromocytoma benign								X							X		X							6		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Adenoma								X																4		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Pars distalis, adenoma				X	X			X	X	X		X			X	X					X			16		
Pars intermedia, adenoma																								1		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
C-cell, adenoma		X			X																			2		
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Penis											+													1		
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Adenoma										X						X								3		
Carcinoma															X				X			X	X	5		

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	3	3	3	4	4	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7
	0	8	8	3	7	7	7	7	9	0	0	2	4	4	5	6	6	9	9	0	1	1	1	1	1	1
	9	8	8	4	3	1	4	9	5	2	4	5	0	4	6	7	7	2	5	1	5	8	8	9	9	9
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	1	3	4	2	4	4	1	1	1	0	3	0	3	4	1	4	0	0	2	4	0	1	0	1	1
	5	2	4	5	3	1	8	5	1	0	7	6	4	8	3	9	4	2	1	2	9	5	6	3	3	3
Genital System (continued)																										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Bilateral, interstitial cell, adenoma									X		X	X	X	X		X	X	X			X		X	X	X	X
Interstitial cell, adenoma						X	X	X						X				X	X							
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Lymph node	+				+	+	+			+	+	+	+		+		+			+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																							X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																X										
Squamous cell papilloma																										
Subcutaneous tissue, fibroma												X				X										
Subcutaneous tissue, lipoma																									X	
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																								+		
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Osteosarcoma, metastatic, nose												X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma												X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Zymbal's gland																+										
Carcinoma																X										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Leukemia mononuclear	X				X	X		X	X	X	X	X	X		X		X			X	X	X	X	X		
Mesothelioma benign																										
Mesothelioma malignant																										

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7			
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total		
	0	0	0	1	1	1	2	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	5	Tissues/ Tumors		
	6	8	9	4	7	8	0	1	4	6	7	8	9	0	1	2	3	5	7	9	0	2	6	7	0		
Genital System (continued)																											
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X		X	X		X	X	X	X	X	X	X	X	X	X		X	X	33		
Interstitial cell, adenoma				X						X		X													9		
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Histiocytic sarcoma																						X			1		
Lymph node			+						+					+	+									+	20		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Fibroadenoma													X		X	X									4		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Keratoacanthoma			X					X				X			X							X			6		
Squamous cell papilloma								X				X						X	X						4		
Subcutaneous tissue, fibroma										X	X														4		
Subcutaneous tissue, lipoma																									1		
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Spinal cord																									1		
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Alveolar/bronchiolar adenoma																											

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

TABLE A2

	4	4	4	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Number of Days on Study	4	5	6	3	5	9	0	0	0	1	2	2	2	4	4	6	6	6	6	6	6	6	7	7	8
	4	5	6	8	3	8	4	4	7	8	0	5	8	1	2	4	5	5	6	6	6	7	3	7	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9	9	5	7	9	6	7	8	7	8	0	8	7	5	6	9	6	7	5	6	7	9	9	9	6
	4	9	6	7	8	9	9	1	2	7	0	9	1	3	2	1	0	4	2	7	3	0	6	5	6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+	+	+	+	+	+	+		+	+	+		+			+		+	+	+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+
Spleen	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																							X		
Squamous cell papilloma																									
Trichoepithelioma																									
Subcutaneous tissue, fibroma						X																		X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma malignant		X																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland																									
Carcinoma, metastatic, Zymbal s gland</																									

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

TABLE A2

Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	2	4	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7
	6	8	2	2	3	3	8	8	8	9	0	2	3	4	4	4	4	6	6	7	7	0	0	0	1
	9	6	5	9	4	8	0	5	9	6	9	7	2	0	4	8	8	2	9	3	9	0	0	8	9
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	1	3	1	4	2	4	1	3	0	0	4	5	4	3	0	3	3	2	2	4	1	1	2	1	3
	7	8	5	9	3	7	3	3	4	8	6	0	2	4	9	0	1	9	0	8	6	8	1	4	7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Mesentery															+		+				+	+			
Oral mucosa																									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign									X			X					X	X		X	X				X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X		X		X	X					X			X									X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																		X	X	X	X	X	X	X	X
Interstitial cell, adenoma																									

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

[illegible]

TABLE A2

Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

	2	4	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7
Number of Days on Study	6	8	2	2	3	3	8	8	8	9	0	2	3	4	4	4	4	6	6	7	7	0	0	0	1
	9	6	5	9	4	8	0	5	9	6	9	7	2	0	4	8	8	2	9	3	9	0	0	8	9
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	1	3	1	4	2	4	1	3	0	0	4	5	4	3	0	3	3	2	2	4	1	1	2	1	3
	7	8	5	9	3	7	3	3	4	8	6	0	2	4	9	0	1	9	0	8	6	8	1	4	7
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Melanoma malignant, metastatic, skin																									
Lymph node					+	+		+	+	+	+	+	+			+		+		+	+		+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma							X								X										X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Keratoacanthoma, multiple																									X
Squamous cell papilloma																									
Pinna, melanoma malignant																									
Subcutaneous tissue, fibroma								X												X					
Subcutaneous tissue, lipoma						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Melanoma malignant, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Renal tubule, adenoma, multiple																									X
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X			X	X	X	X		X		X	X	X	X		X	X		X		X
Mesothelioma benign																									

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

[illegible]

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

[illegible]

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7		
	8	9	9	9	9	0	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	5	1	1	7	7	0	7	9	9	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2		
	6	7	9	6	7	5	9	7	8	5	5	6	6	7	7	7	8	8	8	8	8	9	9	9		
	8	3	0	1	5	8	4	6	1	7	9	4	7	2	8	9	2	4	5	6	9	3	6	7		
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Intestine large, colon	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Intestine large, cecum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Intestine small, duodenum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Intestine small, jejunum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Intestine small, ileum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Cholangiocarcinoma																									1	
Hepatocellular adenoma						X																X			2	
Hepatocellular adenoma, multiple																		X							1	
Mesentery				+								+	+												8	
Pancreas	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Acinus, adenoma																							X		1	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Stomach, forestomach	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Stomach, glandular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Tongue	+																								1	
Squamous cell papilloma	X																								1	
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Pheochromocytoma complex																							X		1	
Pheochromocytoma benign																										

TABLE A2

[illegible]

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

[illegible]

TABLE A3
Statistical Analysis of Primary Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate ^a	17/50 (34%)	3/49 (6%)	14/50 (28%)	4/49 (8%)
Adjusted rate ^b	40.4%	7.5%	32.8%	10.6%
Terminal rate ^c	11/25 (44%)	1/20 (5%)	7/25 (28%)	3/16 (19%)
First incidence (days)	571	628	585	675
Poly-3 test ^d	P=0.014N	P<0.001N	P=0.306N	P=0.002N
Adrenal Medulla: Benign or Complex Pheochromocytoma				
Overall rate	17/50 (34%)	3/49 (6%)	14/50 (28%)	5/49 (10%)
Adjusted rate	40.4%	7.5%	32.8%	13.3%
Terminal rate	11/25 (44%)	1/20 (5%)	7/25 (28%)	4/16 (25%)
First incidence (days)	571	628	585	675
Poly-3 test	P=0.030N	P<0.001N	P=0.306N	P=0.005N
Kidney (Renal Tubule): Adenoma (Single Sections)				
Overall rate	1/50 (2%)	0/48 (0%)	2/50 (4%)	6/49 (12%)
Adjusted rate	2.4%	0.0%	4.9%	15.9%
Terminal rate	1/25 (4%)	0/20 (0%)	1/25 (4%)	2/16 (13%)
First incidence (days)	722 (T)	^e	708	644
Poly-3 test	P=0.003	P=0.510N	P=0.498	P=0.042
Kidney (Renal Tubule): Adenoma or Carcinoma (Single Sections)				
Overall rate	1/50 (2%)	1/48 (2%)	2/50 (4%)	6/49 (12%)
Adjusted rate	2.4%	2.6%	4.9%	15.9%
Terminal rate	1/25 (4%)	1/20 (5%)	1/25 (4%)	2/16 (13%)
First incidence (days)	722 (T)	722 (T)	708	644
Poly-3 test	P=0.008	P=0.750	P=0.498	P=0.042
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	2/50 (4%)	3/48 (6%)	6/50 (12%)	10/49 (20%)
Adjusted rate	4.9%	7.6%	14.5%	26.3%
Terminal rate	2/25 (8%)	2/20 (10%)	3/25 (12%)	5/16 (31%)
First incidence (days)	722 (T)	673	627	644
Poly-3 test	P=0.002	P=0.480	P=0.133	P=0.008
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	2/50 (4%)	4/48 (8%)	6/50 (12%)	10/49 (20%)
Adjusted rate	4.9%	10.2%	14.5%	26.3%
Terminal rate	2/25 (8%)	3/20 (15%)	3/25 (12%)	5/16 (31%)
First incidence (days)	722 (T)	673	627	644
Poly-3 test	P=0.003	P=0.316	P=0.133	P=0.008
Liver: Hepatocellular Adenoma				
Overall rate	1/50 (2%)	1/49 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rate	2.4%	2.5%	0.0%	7.8%
Terminal rate	0/25 (0%)	1/20 (5%)	0/25 (0%)	1/16 (6%)
First incidence (days)	718	722 (T)		622
Poly-3 test	P=0.153	P=0.754	P=0.501N	P=0.283
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	1/50 (2%)	1/49 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.4%	2.5%	2.4%	7.8%
Terminal rate	0/25 (0%)	1/20 (5%)	1/25 (4%)	1/16 (6%)
First incidence (days)	718	722 (T)		622
Poly-3 test	P=0.153	P=0.754	P=0.760	P=0.283

TABLE A3
Statistical Analysis of Primary Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/50 (2%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rate	2.4%	0.0%	0.0%	10.4%
Terminal rate	1/25 (4%)	0/20 (0%)	0/25 (0%)	3/16 (19%)
First incidence (days)	722 (T)			697
Poly-3 test	P=0.024	P=0.503N	P=0.501N	P=0.157
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted rate	2.4%	0.0%	4.9%	10.4%
Terminal rate	1/25 (4%)	0/20 (0%)	2/25 (8%)	3/16 (19%)
First incidence (days)	722 (T)		722 (T)	697
Poly-3 test	P=0.033	P=0.503N	P=0.498	P=0.157
Mammary Gland: Fibroadenoma				
Overall rate	4/50 (8%)	3/50 (6%)	6/50 (12%)	4/50 (8%)
Adjusted rate	9.7%	7.4%	14.4%	10.4%
Terminal rate	3/25 (12%)	2/20 (10%)	3/25 (12%)	1/16 (6%)
First incidence (days)	718	708	538	681
Poly-3 test	P=0.439	P=0.507N	P=0.378	P=0.609
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	4/50 (8%)	4/50 (8%)	6/50 (12%)	4/50 (8%)
Adjusted rate	9.7%	9.9%	14.4%	10.4%
Terminal rate	3/25 (12%)	3/20 (15%)	3/25 (12%)	1/16 (6%)
First incidence (days)	718	708	538	681
Poly-3 test	P=0.487	P=0.637	P=0.378	P=0.609
Pancreatic Islets: Adenoma				
Overall rate	4/50 (8%)	2/48 (4%)	1/50 (2%)	0/49 (0%)
Adjusted rate	9.6%	5.1%	2.4%	0.0%
Terminal rate	1/25 (4%)	2/20 (10%)	1/25 (4%)	0/16 (0%)
First incidence (days)	625	722 (T)	722 (T)	
Poly-3 test	P=0.033N	P=0.366N	P=0.184N	P=0.075N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	16/50 (32%)	13/50 (26%)	12/50 (24%)	11/50 (22%)
Adjusted rate	36.9%	31.0%	27.0%	26.6%
Terminal rate	9/25 (36%)	7/20 (35%)	5/25 (20%)	3/16 (19%)
First incidence (days)	434	628	269	428
Poly-3 test	P=0.177N	P=0.365N	P=0.221N	P=0.215N
Preputial Gland: Adenoma				
Overall rate	3/50 (6%)	0/47 (0%)	7/49 (14%)	2/48 (4%)
Adjusted rate	7.2%	0.0%	16.7%	5.4%
Terminal rate	2/25 (8%)	0/19 (0%)	4/25 (16%)	2/16 (13%)
First incidence (days)	604		529	722 (T)
Poly-3 test	P=0.427	P=0.134N	P=0.158	P=0.556N
Preputial Gland: Carcinoma				
Overall rate	5/50 (10%)	2/47 (4%)	0/49 (0%)	1/48 (2%)
Adjusted rate	11.9%	5.3%	0.0%	2.7%
Terminal rate	4/25 (16%)	2/19 (11%)	0/25 (0%)	1/16 (6%)
First incidence (days)	388	722 (T)		722 (T)
Poly-3 test	P=0.046N	P=0.255N	P=0.034N	P=0.133N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Preputial Gland: Adenoma or Carcinoma				
Overall rate	8/50 (16%)	2/47 (4%)	7/49 (14%)	3/48 (6%)
Adjusted rate	18.9%	5.3%	16.7%	8.2%
Terminal rate	6/25 (24%)	2/19 (11%)	4/25 (16%)	3/16 (19%)
First incidence (days)	388	722 (T)	529	722 (T)
Poly-3 test	P=0.212N	P=0.063N	P=0.511N	P=0.146N
Skin: Squamous Cell Papilloma				
Overall rate	4/50 (8%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	9.7%	2.5%	2.4%	0.0%
Terminal rate	4/25 (16%)	1/20 (5%)	1/25 (4%)	0/16 (0%)
First incidence (days)	722 (T)	722 (T)	722 (T)	
Poly-3 test	P=0.035N	P=0.181N	P=0.179N	P=0.069N
Skin: Keratoacanthoma				
Overall rate	6/50 (12%)	4/50 (8%)	2/50 (4%)	5/50 (10%)
Adjusted rate	14.5%	9.8%	4.9%	12.9%
Terminal rate	5/25 (20%)	2/20 (10%)	1/25 (4%)	1/16 (6%)
First incidence (days)	656	673	708	670
Poly-3 test	P=0.474N	P=0.378N	P=0.134N	P=0.548N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	8/50 (16%)	5/50 (10%)	3/50 (6%)	5/50 (10%)
Adjusted rate	19.3%	12.3%	7.3%	12.9%
Terminal rate	7/25 (28%)	3/20 (15%)	2/25 (8%)	1/16 (6%)
First incidence (days)	656	673	708	670
Poly-3 test	P=0.250N	P=0.282N	P=0.099N	P=0.318N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Basal Cell Adenoma				
Overall rate	8/50 (16%)	6/50 (12%)	3/50 (6%)	7/50 (14%)
Adjusted rate	19.3%	14.7%	7.3%	18.1%
Terminal rate	7/25 (28%)	4/20 (20%)	2/25 (8%)	2/16 (13%)
First incidence (days)	656	673	708	670
Poly-3 test	P=0.474N	P=0.396N	P=0.099N	P=0.556N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	4/50 (8%)	2/50 (4%)	4/50 (8%)	0/50 (0%)
Adjusted rate	9.6%	4.8%	9.6%	0.0%
Terminal rate	2/25 (8%)	0/20 (0%)	2/25 (8%)	0/16 (0%)
First incidence (days)	625	553	580	
Poly-3 test	P=0.092N	P=0.341N	P=0.642	P=0.071N
Testes: Adenoma				
Overall rate	42/49 (86%)	43/49 (88%)	43/49 (88%)	43/48 (90%)
Adjusted rate	93.0%	90.2%	93.2%	95.6%
Terminal rate	23/25 (92%)	18/20 (90%)	24/25 (96%)	16/16 (100%)
First incidence (days)	473	444	529	444
Poly-3 test	P=0.275	P=0.450N	P=0.662	P=0.464
Thyroid Gland (C-cell): Adenoma				
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	2/49 (4%)
Adjusted rate	4.9%	2.5%	7.3%	5.2%
Terminal rate	2/25 (8%)	1/20 (5%)	3/25 (12%)	2/16 (13%)
First incidence (days)	722 (T)	722 (T)	722 (T)	722 (T)
Poly-3 test	P=0.466	P=0.505N	P=0.497	P=0.668

TABLE A3
Statistical Analysis of Primary Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	2/49 (4%)
Adjusted rate	4.9%	4.9%	7.3%	5.2%
Terminal rate	2/25 (8%)	1/20 (5%)	3/25 (12%)	2/16 (13%)
First incidence (days)	722 (T)	666	722 (T)	722 (T)
Poly-3 test	P=0.531	P=0.691	P=0.497	P=0.668
All Organs: Mononuclear Cell Leukemia				
Overall rate	29/50 (58%)	32/50 (64%)	26/50 (52%)	27/50 (54%)
Adjusted rate	62.7%	67.8%	57.4%	59.7%
Terminal rate	13/25 (52%)	11/20 (55%)	12/25 (48%)	7/16 (44%)
First incidence (days)	309	466	529	444
Poly-3 test	P=0.317N	P=0.378	P=0.381N	P=0.468N
All Organs: Benign Neoplasms				
Overall rate	47/50 (94%)	46/50 (92%)	48/50 (96%)	49/50 (98%)
Adjusted rate	99.2%	93.4%	98.0%	100.0%
Terminal rate	25/25 (100%)	19/20 (95%)	25/25 (100%)	16/16 (100%)
First incidence (days)	434	444	269	428
Poly-3 test	P=0.228	P=0.136N	P=0.712N	P=0.996
All Organs: Malignant Neoplasms				
Overall rate	34/50 (68%)	40/50 (80%)	29/50 (58%)	29/50 (58%)
Adjusted rate	71.8%	81.5%	63.1%	63.9%
Terminal rate	16/25 (64%)	14/20 (70%)	14/25 (56%)	8/16 (50%)
First incidence (days)	309	444	486	444
Poly-3 test	P=0.091N	P=0.182	P=0.243N	P=0.270N
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	49/50 (98%)	49/50 (98%)	49/50 (98%)
Adjusted rate	99.7%	98.3%	98.6%	100.0%
Terminal rate	25/25 (100%)	20/20 (100%)	25/25 (100%)	16/16 (100%)
First incidence (days)	309	444	269	428
Poly-3 test	P=0.580	P=0.656N	P=0.760N	P=1.000

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, liver, lung, pancreatic islets, pituitary gland, preputial gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by N.

^e Not applicable; no neoplasms in animal group

TABLE A4
Historical Incidence of Renal Tubule Neoplasms in Untreated Male F344/N Rats^a

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	1/327 (0.3%)	0/327	1/327 (0.3%)
Standard deviation	0.8%		0.8%
Range	0%-2%		0%-2%

^a Data as of 1 August 1997

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine^a

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	13	15	10
Natural deaths	14	17	10	24
Survivors				
Terminal sacrifice	25	20	25	16
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(48)	(50)	(49)
Hyperplasia, lymphoid			1 (2%)	
Inflammation, acute			1 (2%)	
Inflammation, chronic			1 (2%)	
Parasite metazoan	4 (8%)	4 (8%)	3 (6%)	2 (4%)
Intestine large, rectum	(50)	(48)	(50)	(49)
Edema		1 (2%)		
Parasite metazoan	4 (8%)	2 (4%)		1 (2%)
Intestine large, cecum	(49)	(47)	(50)	(49)
Edema		1 (2%)		
Hyperplasia, lymphoid		1 (2%)		
Inflammation, acute	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic active		1 (2%)		
Parasite metazoan			1 (2%)	1 (2%)
Ulcer	1 (2%)			
Intestine small, duodenum	(50)	(47)	(50)	(48)
Ectopic pancreas			1 (2%)	
Intestine small, jejunum	(50)	(47)	(50)	(47)
Congestion		1 (2%)		
Intestine small, ileum	(50)	(47)	(50)	(47)
Fibrosis	1 (2%)			
Hyperplasia, lymphoid	6 (12%)	9 (19%)	3 (6%)	4 (9%)
Liver	(50)	(49)	(50)	(50)
Angiectasis		1 (2%)	1 (2%)	1 (2%)
Basophilic focus	12 (24%)	5 (10%)		1 (2%)
Clear cell focus	7 (14%)	1 (2%)	7 (14%)	4 (8%)
Congestion	1 (2%)			
Degeneration, cystic	4 (8%)	12 (24%)	11 (22%)	3 (6%)
Developmental malformation			1 (2%)	1 (2%)
Eosinophilic focus	14 (28%)	23 (47%)	23 (46%)	13 (26%)
Fibrosis	1 (2%)	1 (2%)	1 (2%)	10 (20%)
Hematopoietic cell proliferation	2 (4%)	1 (2%)		
Hepatodiaphragmatic nodule	3 (6%)	1 (2%)		
Mitotic alteration				2 (4%)
Mixed cell focus	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Necrosis	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Pigmentation	4 (8%)	11 (22%)	20 (40%)	25 (50%)
Thrombosis			1 (2%)	
Vacuolization cytoplasmic	4 (8%)	6 (12%)	13 (26%)	17 (34%)
Bile duct, hyperplasia	46 (92%)	43 (88%)	44 (88%)	49 (98%)
Centrilobular, cytomegaly		4 (8%)	8 (16%)	6 (12%)
Centrilobular, degeneration	1 (2%)	3 (6%)	2 (4%)	8 (16%)
Centrilobular, necrosis		3 (6%)		5 (10%)
Periportal, fibrosis			2 (4%)	29 (58%)

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Alimentary System (continued)				
Mesentery	(11)	(14)	(7)	(8)
Cyst	1 (9%)			
Hemorrhage			1 (14%)	
Inflammation, acute		1 (7%)		
Fat, necrosis	10 (91%)	13 (93%)	6 (86%)	8 (100%)
Oral mucosa	(1)		(2)	
Pharyngeal, hyperplasia			1 (50%)	
Pancreas	(50)	(48)	(50)	(49)
Atrophy	18 (36%)	15 (31%)	17 (34%)	12 (24%)
Cytoplasmic alteration	2 (4%)			
Hyperplasia	2 (4%)	4 (8%)	2 (4%)	3 (6%)
Inflammation, chronic	1 (2%)		3 (6%)	
Acinus, hyperplasia		1 (2%)		
Artery, inflammation, acute	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Cellular alteration				1 (2%)
Inflammation, chronic active		1 (2%)		
Stomach, forestomach	(50)	(49)	(50)	(49)
Hyperkeratosis				2 (4%)
Inflammation, acute		1 (2%)		1 (2%)
Inflammation, chronic active	2 (4%)			8 (16%)
Ulcer	2 (4%)	10 (20%)	3 (6%)	4 (8%)
Epithelium, hyperplasia, squamous	1 (2%)	7 (14%)	7 (14%)	11 (22%)
Stomach, glandular	(50)	(49)	(50)	(49)
Erosion	15 (30%)	17 (35%)	12 (24%)	12 (24%)
Inflammation, acute				1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)		
Inflammation, chronic active			1 (2%)	1 (2%)
Mineralization		2 (4%)	2 (4%)	8 (16%)
Necrosis				1 (2%)
Ulcer	2 (4%)	5 (10%)	1 (2%)	1 (2%)
Tooth	(2)	(1)	(1)	
Dysplasia		1 (100%)		
Inflammation, acute	1 (50%)			
Inflammation, chronic active	1 (50%)		1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	45 (90%)	43 (86%)	43 (86%)	46 (92%)
Mineralization	1 (2%)		3 (6%)	2 (4%)
Thrombosis	2 (4%)	6 (12%)	3 (6%)	4 (8%)
Coronary artery, inflammation, chronic active		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)			1 (2%)
Congestion			1 (2%)	
Hyperplasia	8 (16%)	7 (14%)	7 (14%)	2 (4%)
Hypertrophy	1 (2%)			2 (4%)
Vacuolization cytoplasmic	9 (18%)	5 (10%)	9 (18%)	7 (14%)
Adrenal medulla	(50)	(49)	(50)	(49)
Hyperplasia	17 (34%)	22 (45%)	19 (38%)	15 (31%)
Bilateral, hyperplasia	1 (2%)	1 (2%)		1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Endocrine System (continued)				
Islets, pancreatic	(50)	(48)	(50)	(49)
Hyperplasia	5 (10%)	2 (4%)	1 (2%)	1 (2%)
Parathyroid gland	(50)	(50)	(50)	(48)
Hyperplasia		1 (2%)	3 (6%)	3 (6%)
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, angiectasis		2 (4%)	2 (4%)	2 (4%)
Pars distalis, cyst	2 (4%)	8 (16%)	3 (6%)	1 (2%)
Pars distalis, degeneration				1 (2%)
Pars distalis, ectasia		1 (2%)		
Pars distalis, hemorrhage	1 (2%)			
Pars distalis, hyperplasia	22 (44%)	16 (32%)	18 (36%)	12 (24%)
Pars distalis, thrombosis		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(49)
Pigmentation		1 (2%)		
Ultimobranchial cyst	1 (2%)	1 (2%)		1 (2%)
C-cell, hyperplasia	7 (14%)	5 (10%)	3 (6%)	3 (6%)
Follicle, dilatation	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Follicular cell, hyperplasia	1 (2%)	5 (10%)	1 (2%)	2 (4%)
General Body System				
None				
Genital System				
Epididymis	(49)	(49)	(49)	(48)
Fibrosis			1 (2%)	
Inflammation, chronic			2 (4%)	
Penis	(1)			
Inflammation, chronic active	1 (100%)			
Preputial gland	(50)	(47)	(49)	(48)
Atrophy	1 (2%)			
Hyperplasia	4 (8%)	3 (6%)	5 (10%)	4 (8%)
Inflammation, acute	2 (4%)			2 (4%)
Inflammation, chronic	17 (34%)	25 (53%)	17 (35%)	23 (48%)
Inflammation, chronic active	5 (10%)	14 (30%)	14 (29%)	5 (10%)
Duct, dilatation		2 (4%)		2 (4%)
Prostate	(50)	(48)	(50)	(49)
Hemorrhage, chronic		1 (2%)		
Hyperplasia, focal	1 (2%)	1 (2%)	4 (8%)	2 (4%)
Inflammation, acute	2 (4%)	2 (4%)		1 (2%)
Inflammation, chronic	2 (4%)	1 (2%)	4 (8%)	3 (6%)
Inflammation, chronic active	31 (62%)	29 (60%)	24 (48%)	22 (45%)
Seminal vesicle	(50)	(47)	(50)	(48)
Dilatation			1 (2%)	
Fibrosis				1 (2%)
Inflammation, acute		1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)			1 (2%)
Inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Mineralization				1 (2%)
Testes	(49)	(49)	(49)	(48)
Atrophy	2 (4%)			
Necrosis	1 (2%)			
Thrombosis			1 (2%)	
Bilateral, interstitial cell, hyperplasia	3 (6%)	2 (4%)	3 (6%)	1 (2%)
Interstitial cell, hyperplasia	9 (18%)	6 (12%)	6 (12%)	4 (8%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Depletion cellular	2 (4%)	4 (8%)	3 (6%)	1 (2%)
Fibrosis			1 (2%)	1 (2%)
Hemorrhage		1 (2%)		
Lymph node	(20)	(25)	(20)	(23)
Iliac, hyperplasia, lymphoid	1 (5%)	1 (4%)		
Iliac, infiltration cellular, plasma cell	1 (5%)			
Mediastinal, congestion		5 (20%)		4 (17%)
Mediastinal, ectasia			1 (5%)	
Mediastinal, hemorrhage	1 (5%)	1 (4%)	2 (10%)	
Mediastinal, hyperplasia, lymphoid				1 (4%)
Mediastinal, pigmentation			1 (5%)	
Pancreatic, congestion			1 (5%)	2 (9%)
Pancreatic, edema				1 (4%)
Pancreatic, hyperplasia, lymphoid			1 (5%)	
Pancreatic, inflammation, chronic active				1 (4%)
Pancreatic, necrosis			1 (5%)	
Pancreatic, pigmentation			1 (5%)	
Renal, congestion	1 (5%)		1 (5%)	3 (13%)
Renal, edema			1 (5%)	
Renal, fibrosis		1 (4%)		
Renal, hyperplasia, lymphoid			2 (10%)	
Renal, pigmentation			1 (5%)	4 (17%)
Lymph node, mandibular	(50)	(50)	(50)	(50)
Congestion		1 (2%)	1 (2%)	
Ectasia	4 (8%)	3 (6%)	2 (4%)	3 (6%)
Hyperplasia, lymphoid			1 (2%)	
Inflammation, chronic active		1 (2%)		
Lymph node, mesenteric	(50)	(47)	(50)	(48)
Congestion		2 (4%)		1 (2%)
Ectasia	2 (4%)	3 (6%)	2 (4%)	1 (2%)
Fibrosis			2 (4%)	
Hemorrhage		1 (2%)		1 (2%)
Inflammation, acute	1 (2%)			
Necrosis		3 (6%)		
Spleen	(49)	(48)	(50)	(49)
Atrophy			1 (2%)	
Congestion		1 (2%)		1 (2%)
Fibrosis	14 (29%)	11 (23%)	9 (18%)	12 (24%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)		1 (2%)
Hyperplasia, focal			1 (2%)	
Necrosis	4 (8%)	2 (4%)	1 (2%)	
Pigmentation				2 (4%)
Thrombosis		1 (2%)		
Thymus	(50)	(49)	(48)	(50)
Cyst	1 (2%)			
Ectopic parathyroid gland				1 (2%)
Fibrosis		1 (2%)		
Hemorrhage		1 (2%)		1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Integumentary System				
Mammary gland	(49)	(48)	(50)	(49)
Concretion		1 (2%)		
Galactocele			1 (2%)	
Hyperplasia	1 (2%)	3 (6%)	2 (4%)	3 (6%)
Duct, dilatation	14 (29%)	16 (33%)	12 (24%)	15 (31%)
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion			2 (4%)	
Hyperkeratosis			1 (2%)	
Hyperplasia, squamous		1 (2%)	1 (2%)	
Inflammation, acute		1 (2%)		
Necrosis			1 (2%)	
Epidermis, degeneration				1 (2%)
Subcutaneous tissue, inflammation, chronic active			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	2 (4%)	1 (2%)	4 (8%)	6 (12%)
Hyperostosis		1 (2%)		
Osteomalacia				1 (2%)
Osteopetrosis	1 (2%)		2 (4%)	
Nervous System				
Brain	(50)	(50)	(48)	(50)
Hemorrhage			1 (2%)	
Hydrocephalus	1 (2%)			
Inflammation, acute				1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion		1 (2%)		2 (4%)
Hemorrhage			2 (4%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		
Infiltration cellular, histiocyte	6 (12%)	4 (8%)	9 (18%)	9 (18%)
Inflammation, chronic	8 (16%)	10 (20%)	12 (24%)	9 (18%)
Metaplasia, osseous				1 (2%)
Alveolar epithelium, hyperplasia		3 (6%)		3 (6%)
Nose	(50)	(50)	(49)	(50)
Cyst		1 (2%)	1 (2%)	
Cyst epithelial inclusion				1 (2%)
Inflammation, chronic			1 (2%)	
Inflammation, chronic active	26 (52%)	18 (36%)	21 (43%)	25 (50%)
Polyp inflammatory				1 (2%)
Nasolacrimal duct, cyst			1 (2%)	1 (2%)
Nasolacrimal duct, inflammation, acute	1 (2%)			1 (2%)
Squamous epithelium, nasolacrimal duct, hyperplasia		1 (2%)		
Special Senses System				
Eye		(1)		
Atrophy		1 (100%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Urinary System				
Kidney	(50)	(48)	(50)	(49)
Atrophy			1 (2%)	
Cyst	3 (6%)	3 (6%)	13 (26%)	10 (20%)
Developmental malformation	2 (4%)			
Hydronephrosis	3 (6%)	1 (2%)		2 (4%)
Inflammation, acute				1 (2%)
Nephropathy	47 (94%)	47 (98%)	49 (98%)	49 (100%)
Pigmentation				1 (2%)
Artery, inflammation, acute	1 (2%)			
Artery, inflammation, chronic active	1 (2%)			
Capsule, hemorrhage, chronic		1 (2%)		
Pelvis, inflammation, acute				1 (2%)
Renal tubule, hyperplasia	1 (2%)		4 (8%)	7 (14%)
Urinary bladder	(50)	(47)	(50)	(49)
Hemorrhage		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	4 (8%)		1 (2%)	1 (2%)

APPENDIX B

SUMMARY OF LESIONS IN FEMALE F344/N RATS IN THE 2-YEAR DRINKING WATER STUDY OF PYRIDINE

TABLE B1	Summary of the Incidence of Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine	B-2
TABLE B2	Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine	B-6
TABLE B3	Statistical Analysis of Primary Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine	B-24
TABLE B4	Historical Incidence of Leukemias in Untreated Female F344/N Rats	B-27
TABLE B5	Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine	B-28

TABLE B1
Summary of the Incidence of Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine^a

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	3	8	7	2
Natural deaths	15	5	14	22
Survivors				
Terminal sacrifice	32	37	29	26
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Schwannoma malignant, metastatic, uterus		1 (2%)		
Intestine large, colon	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Intestine large, cecum	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Intestine small, duodenum	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas		1 (2%)		
Carcinoma, metastatic, uterus		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Intestine small, jejunum	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Intestine small, ileum	(50)	(49)	(50)	(50)
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Carcinoma, metastatic, pancreas		1 (2%)		
Carcinoma, metastatic, uterus		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Hepatocellular adenoma	1 (2%)		1 (2%)	
Mesentery	(9)	(11)	(7)	(12)
Carcinoma, metastatic, uterus		1 (9%)		
Fibrous histiocytoma	1 (11%)			
Schwannoma malignant, metastatic, uterus		1 (9%)		
Oral mucosa	(2)	(1)		(2)
Pharyngeal, squamous cell carcinoma	2 (100%)			
Pharyngeal, squamous cell papilloma				1 (50%)
Pancreas	(49)	(50)	(50)	(50)
Carcinoma		2 (4%)		
Carcinoma, metastatic, uterus		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Acinus, adenoma		1 (2%)		1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)
Carcinoma, metastatic, uterus		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Tongue			(1)	(2)
Squamous cell papilloma				1 (50%)
Cardiovascular System				
Heart	(49)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		

TABLE B1
Summary of the Incidence of Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Adrenal medulla	(50)	(50)	(50)	(49)
Pheochromocytoma benign	2 (4%)		1 (2%)	
Bilateral, pheochromocytoma benign	1 (2%)			
Islets, pancreatic	(49)	(50)	(50)	(50)
Adenoma	1 (2%)		1 (2%)	
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Parathyroid gland	(48)	(50)	(48)	(50)
Pituitary gland	(49)	(50)	(50)	(50)
Pars distalis, adenoma	17 (35%)	12 (24%)	18 (36%)	15 (30%)
Pars distalis, adenoma, multiple	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	3 (6%)	2 (4%)	2 (4%)	
General Body System				
None				
Genital System				
Clitoral gland	(47)	(48)	(50)	(49)
Adenoma	2 (4%)	3 (6%)		1 (2%)
Carcinoma		1 (2%)	1 (2%)	2 (4%)
Bilateral, adenoma			1 (2%)	
Ovary	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Carcinoma, metastatic, pancreas		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Granulosa-theca tumor malignant			1 (2%)	
Uterus	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)		
Carcinoma, metastatic, pancreas		1 (2%)		
Polyp stromal	4 (8%)	7 (14%)	9 (18%)	7 (14%)
Polyp stromal, multiple				1 (2%)
Sarcoma stromal	1 (2%)			
Schwannoma malignant, metastatic, uterus		1 (2%)		
Vagina				(1)
Lipoma				1 (100%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Lymph node	(7)	(9)	(15)	(19)
Mediastinal, carcinoma, metastatic, kidney		1 (11%)		
Mediastinal, carcinoma, metastatic, pancreas		1 (11%)		
Mediastinal, fibrous histiocytoma, metastatic, mesentery	1 (14%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Hematopoietic System (continued)				
Lymph node, mandibular	(49)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Lymph node, mesenteric	(49)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas		1 (2%)		
Carcinoma, metastatic, uterus		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Spleen	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Carcinoma, metastatic, pancreas		1 (2%)		
Carcinoma, metastatic, uterus		1 (2%)		
Thymus	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Carcinoma, metastatic, pancreas		1 (2%)		
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoma	2 (4%)	1 (2%)	1 (2%)	
Carcinoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Fibroadenoma	19 (38%)	15 (30%)	14 (28%)	18 (36%)
Fibroadenoma, multiple	8 (16%)	10 (20%)	6 (12%)	2 (4%)
Sarcoma	1 (2%)			
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma		1 (2%)		
Keratoacanthoma				1 (2%)
Trichoepithelioma				1 (2%)
Musculoskeletal System				
Skeletal muscle	(2)	(1)		
Carcinoma, metastatic, uterus		1 (100%)		
Abdominal, fibrous histiocytoma, metastatic, mesentery	1 (50%)			
Abdominal, lipoma	1 (50%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant	2 (4%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Carcinoma, metastatic, clitoral gland				1 (2%)
Carcinoma, metastatic, kidney		1 (2%)		
Carcinoma, metastatic, mammary gland			1 (2%)	
Carcinoma, metastatic, pancreas		2 (4%)		
Carcinoma, metastatic, uterus		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Pleura		(1)		
Carcinoma, metastatic, kidney		1 (100%)		
Trachea	(50)	(50)	(50)	(50)

TABLE B1
Summary of the Incidence of Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Special Senses System				
Zymbal's gland		(1)		(1)
Carcinoma		1 (100%)		1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas		1 (2%)		
Transitional epithelium, carcinoma		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs ^b	(50)	(50)	(50)	(50)
Leukemia mononuclear	12 (24%)	16 (32%)	22 (44%)	23 (46%)
Lymphoma malignant	1 (2%)			1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms ^c	45	42	45	44
Total primary neoplasms	84	78	80	80
Total animals with benign neoplasms	39	34	35	35
Total benign neoplasms	63	54	55	52
Total animals with malignant neoplasms	21	22	23	28
Total malignant neoplasms	21	24	25	28
Total animals with metastatic neoplasms	1	5	1	1
Total metastatic neoplasms	13	36	1	1

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

	4	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	8	3	4	7	1	4	5	6	6	8	9	1	2	2	2	2	2	2	2	2	2	2	2
	8	3	6	0	1	2	0	6	6	2	5	7	8	9	9	9	9	9	9	9	9	9	9
	2	2	2	3	2	3	2	2	3	3	2	2	3	2	2	2	2	2	2	2	2	2	2
Carcass ID Number	8	7	8	0	8	1	7	9	1	0	6	7	1	6	6	6	7	7	7	7	8	8	8
	0	7	4	0	8	2	8	9	5	1	7	4	1	6	8	9	0	2	3	6	9	1	2
Respiratory System																							
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							
Carcinoma, metastatic, kidney										X													
Carcinoma, metastatic, pancreas				X		X																	
Carcinoma, metastatic, uterus	X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura										+													
Carcinoma, metastatic, kidney										X													
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																							
Zymbal s gland				+																			
Carcinoma				X																			
Urinary System																							
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas						X																	
Transitional epithelium, carcinoma								X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																							
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X						X	X	X		X		X	X			X	X		X

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7			
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3			
	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0			
Carcass ID Number	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	2	2	2	2	2	2	3	Total		
	9	9	9	9	9	9	9	0	0	0	0	0	0	0	1	1	1	7	7	8	8	8	9	9	Tissues/ Tumors		
	1	2	3	4	6	7	8	2	4	5	6	7	8	9	0	3	4	1	5	6	7	9	0	5	3		
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Alveolar/bronchiolar adenoma										X															1		
Carcinoma, metastatic, kidney																									1		
Carcinoma, metastatic, pancreas																									2		
Carcinoma, metastatic, uterus																									1		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Pleura																									1		
Carcinoma, metastatic, kidney																									1		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Special Senses System																											
Zymbal s gland																									1		
Carcinoma																									1		
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Carcinoma, metastatic, pancreas																									1		
Transitional epithelium, carcinoma																									1		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Leukemia mononuclear		X			X		X					X						X						X	16		

TABLE B2

Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	4	5	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
	9	2	4	6	7	8	8	0	2	6	7	8	9	9	0	0	0	0	1	1	2	2	2	2	2
	6	1	9	1	3	0	6	5	4	5	1	7	8	9	0	3	7	7	1	8	1	9	9	9	9
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	3	4	2	5	1	5	6	5	5	3	5	3	4	5	6	2	1	4	5	4	1	1	2	2	2
	9	8	7	3	7	9	3	1	4	4	6	7	6	7	2	0	8	5	0	0	6	9	1	2	3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery	+		+			+								+											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X	X		X					X	X		X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																X									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																			X						
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant															X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal												X					X				X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+	+	+	+		+	+				+	+					+	+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

TABLE B2

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Carcass ID Number	2	2	2	2	2	3	3	3	3	3	3	3	3	4	4	4	4	4	4	5	5	5	6	6	6	6
	4	5	6	8	9	0	1	2	3	5	6	8	1	2	3	4	7	9	2	5	8	0	1	4	5	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Fibroadenoma			X	X			X		X		X					X	X		X						X	14
Fibroadenoma, multiple														X				X		X						6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Carcinoma, metastatic, mammary gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye												+														1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X		X	X					X		X				X								22

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

	3	4	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7		
Number of Days on Study	8	5	0	1	8	8	8	0	0	0	0	1	2	2	3	3	3	4	4	7	7	8	9	0	1	2
	0	7	3	1	3	4	9	3	5	8	6	5	8	4	6	9	1	9	2	3	7	2	5	1	9	
	3	3	3	3	4	4	3	3	4	3	3	3	3	4	4	3	4	3	3	3	4	4	3	3	3	
Carcass ID Number	9	7	7	6	0	1	7	9	0	8	6	9	9	0	1	9	0	9	9	6	0	0	8	9	6	
	4	4	2	7	4	3	8	6	1	2	8	8	9	3	4	3	9	7	1	9	2	5	1	0	6	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesentery	+					+								+				+	+				+	+		
Oral mucosa																										
Pharyngeal, squamous cell papilloma																										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Acinus, adenoma																										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Tongue																										
Squamous cell papilloma																										
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pars distalis, adenoma																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																										
Carcinoma																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Polyp stromal																										
Polyp stromal, multiple																										
Vagina																										
Lipoma																										

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

TABLE B2

Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	3	4	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7			
	8	5	0	1	8	8	8	0	0	0	1	2	2	3	3	3	4	4	7	7	8	9	0	1	2		
	0	7	3	1	3	4	9	3	5	8	6	5	8	4	6	9	1	9	2	3	7	2	5	1	9		
Carcass ID Number	3	3	3	3	4	4	3	3	4	3	3	3	3	4	4	3	4	3	3	3	4	4	3	3	3		
	9	7	7	6	0	1	7	9	0	8	6	9	9	0	1	9	0	9	9	6	0	0	8	9	6		
	4	4	2	7	4	3	8	6	1	2	8	8	9	3	4	3	9	7	1	9	2	5	1	0	6		
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lymph node	+				+	+			+	+	+			+	+	+	+		+	+	+		+	+			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Carcinoma																											
Fibroadenoma								X		X								X			X						
Fibroadenoma, multiple												X															
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Keratoacanthoma																											
Trichoepithelioma																											
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Alveolar/bronchiolar adenoma													X														
Carcinoma, metastatic, clitoral gland																											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Special Senses System																											
Eye																											
Zymbal s gland																											
Carcinoma																											
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Leukemia mononuclear	X				X	X		X	X	X	X		X	X	X	X	X	X		X		X	X	X	X		
Lymphoma malignant																											

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7		
Number of Days on Study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	
	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4	3	
Carcass ID Number	7	7	7	7	7	7	8	8	8	8	8	8	8	8	8	8	9	9	0	0	0	0	1	1	1	1	
	0	1	3	6	7	9	0	3	4	5	6	7	8	9	2	5	0	6	7	8	0	1	2	5	5	Total Tissues/ Tumors	
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymph node	+										+									+		+				19	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Carcinoma								X																		1	
Fibroadenoma	X		X	X	X		X		X	X		X	X		X					X	X	X		X		18	
Fibroadenoma, multiple																		X								2	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Keratoacanthoma																									X	1	
Trichoepithelioma													X													1	
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Alveolar/bronchiolar adenoma																								X		2	
Carcinoma, metastatic, clitoral gland										X																1	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Special Senses System																											
Eye						+	+																			2	
Zymbal s gland																								+		1	
Carcinoma																								X		1	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leukemia mononuclear	X		X	X							X									X						23	
Lymphoma malignant													X													1	

TABLE B3
Statistical Analysis of Primary Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate ^a	3/50 (6%)	0/50 (0%)	1/50 (2%)	0/49 (0%)
Adjusted rate ^b	6.7%	0.0%	2.3%	0.0%
Terminal rate ^c	2/32 (6%)	0/37 (0%)	1/29 (3%)	0/25 (0%)
First incidence (days)	667	^e	729 (T)	
Poly-3 test ^d	P=0.094N	P=0.114N	P=0.311N	P=0.140N
Clitoral Gland: Adenoma				
Overall rate	2/47 (4%)	3/48 (6%)	1/50 (2%)	1/49 (2%)
Adjusted rate	4.7%	6.8%	2.3%	2.5%
Terminal rate	1/32 (3%)	3/36 (8%)	1/29 (3%)	1/25 (4%)
First incidence (days)	622	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.295N	P=0.521	P=0.487N	P=0.522N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	2/47 (4%)	4/48 (8%)	2/50 (4%)	3/49 (6%)
Adjusted rate	4.7%	9.0%	4.6%	7.6%
Terminal rate	1/32 (3%)	3/36 (8%)	1/29 (3%)	3/25 (12%)
First incidence (days)	622	728	707	729 (T)
Poly-3 test	P=0.483	P=0.359	P=0.680N	P=0.472
Mammary Gland: Fibroadenoma				
Overall rate	27/50 (54%)	25/50 (50%)	20/50 (40%)	20/50 (40%)
Adjusted rate	58.5%	53.7%	44.6%	47.3%
Terminal rate	18/32 (56%)	19/37 (51%)	15/29 (52%)	15/26 (58%)
First incidence (days)	596	666	580	589
Poly-3 test	P=0.139N	P=0.398N	P=0.126N	P=0.193N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	27/50 (54%)	25/50 (50%)	20/50 (40%)	20/50 (40%)
Adjusted rate	58.5%	53.7%	44.6%	47.3%
Terminal rate	18/32 (56%)	19/37 (51%)	15/29 (52%)	15/26 (58%)
First incidence (days)	596	666	580	589
Poly-3 test	P=0.139N	P=0.398N	P=0.126N	P=0.193N
Mammary Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.8%	6.5%	4.5%	2.5%
Terminal rate	2/32 (6%)	1/37 (3%)	0/29 (0%)	1/26 (4%)
First incidence (days)	717	650	699	729 (T)
Poly-3 test	P=0.223N	P=0.646N	P=0.503N	P=0.337N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	27/50 (54%)	26/50 (52%)	21/50 (42%)	21/50 (42%)
Adjusted rate	58.5%	55.5%	46.7%	49.6%
Terminal rate	18/32 (56%)	19/37 (51%)	15/29 (52%)	16/26 (62%)
First incidence (days)	596	650	580	589
Poly-3 test	P=0.191N	P=0.468N	P=0.174N	P=0.262N
Pancreas: Adenoma or Carcinoma				
Overall rate	0/49 (0%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	0.0%	6.4%	0.0%	2.5%
Terminal rate	0/32 (0%)	1/37 (3%)	0/29 (0%)	1/26 (4%)
First incidence (days)		546		729 (T)
Poly-3 test	P=0.609	P=0.131		P=0.486

TABLE B3
Statistical Analysis of Primary Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	18/49 (37%)	12/50 (24%)	18/50 (36%)	15/50 (30%)
Adjusted rate	39.9%	25.8%	40.4%	35.8%
Terminal rate	10/31 (32%)	8/37 (22%)	13/29 (45%)	10/26 (39%)
First incidence (days)	588	642	671	634
Poly-3 test	P=0.509	P=0.110N	P=0.565	P=0.431N
Thyroid Gland (C-cell): Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	6.7%	6.5%	4.6%	0.0%
Terminal rate	1/32 (3%)	2/37 (5%)	1/29 (3%)	0/26 (0%)
First incidence (days)	687	695	707	
Poly-3 test	P=0.087N	P=0.649N	P=0.506N	P=0.135N
Uterus: Stromal Polyp				
Overall rate	4/50 (8%)	7/50 (14%)	9/50 (18%)	8/50 (16%)
Adjusted rate	9.0%	15.3%	20.4%	19.1%
Terminal rate	4/32 (13%)	7/37 (19%)	6/29 (21%)	5/26 (19%)
First incidence (days)	729 (T)	729 (T)	687	503
Poly-3 test	P=0.125	P=0.278	P=0.111	P=0.147
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	5/50 (10%)	7/50 (14%)	9/50 (18%)	8/50 (16%)
Adjusted rate	11.1%	15.3%	20.4%	19.1%
Terminal rate	4/32 (13%)	7/37 (19%)	6/29 (21%)	5/26 (19%)
First incidence (days)	493	729 (T)	687	503
Poly-3 test	P=0.177	P=0.390	P=0.180	P=0.227
All Organs: Mononuclear Cell Leukemia				
Overall rate	12/50 (24%)	16/50 (32%)	22/50 (44%)	23/50 (46%)
Adjusted rate	26.5%	34.3%	45.4%	48.7%
Terminal rate	8/32 (25%)	12/37 (32%)	8/29 (28%)	5/26 (19%)
First incidence (days)	636	546	496	380
Poly-3 test	P=0.013	P=0.279	P=0.043	P=0.020
All Organs: Benign Neoplasms				
Overall rate	39/50 (78%)	34/50 (68%)	35/50 (70%)	35/50 (70%)
Adjusted rate	81.6%	72.5%	77.1%	78.6%
Terminal rate	24/32 (75%)	27/37 (73%)	25/29 (86%)	23/26 (89%)
First incidence (days)	588	642	580	503
Poly-3 test	P=0.511N	P=0.203N	P=0.385N	P=0.459N
All Organs: Malignant Neoplasms				
Overall rate	21/50 (42%)	23/50 (46%)	23/50 (46%)	28/50 (56%)
Adjusted rate	44.3%	46.7%	47.4%	59.3%
Terminal rate	13/32 (41%)	13/37 (35%)	8/29 (28%)	10/26 (39%)
First incidence (days)	399	488	496	380
Poly-3 test	P=0.077	P=0.486	P=0.459	P=0.100

TABLE B3
Statistical Analysis of Primary Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	45/50 (90%)	43/50 (86%)	45/50 (90%)	44/50 (88%)
Adjusted rate	91.2%	86.0%	91.7%	91.0%
Terminal rate	28/32 (88%)	30/37 (81%)	26/29 (90%)	23/26 (89%)
First incidence (days)	399	488	496	380
Poly-3 test	P=0.452	P=0.307N	P=0.613	P=0.627N

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, pancreas, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by N.

^e Not applicable; no neoplasms in animal group

TABLE B4
Historical Incidence of Leukemias in Untreated Female F344/N Rats^a

		Incidence in Controls
Overall Historical Incidence		
Total		102/330 (30.9%)
Standard deviation		10.0%
Range		16%-44%

^a Data as of 1 August 1997; includes data for lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemias

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine^a

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	3	8	7	2
Natural deaths	15	5	14	22
Survivors				
Terminal sacrifice	32	37	29	26
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)	
Parasite metazoan	3 (6%)	3 (6%)	3 (6%)	1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(50)
Parasite metazoan	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Intestine large, cecum	(50)	(50)	(50)	(50)
Inflammation, chronic				1 (2%)
Inflammation, chronic active			1 (2%)	
Parasite metazoan			1 (2%)	
Ulcer		1 (2%)		
Intestine small, duodenum	(50)	(50)	(50)	(50)
Ectopic pancreas	1 (2%)			
Inflammation, chronic active			1 (2%)	
Intestine small, ileum	(50)	(49)	(50)	(50)
Hyperplasia, lymphoid	3 (6%)	2 (4%)	2 (4%)	5 (10%)
Inflammation, chronic active				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Basophilic focus	38 (76%)	28 (56%)	11 (22%)	
Clear cell focus	4 (8%)	9 (18%)	11 (22%)	16 (32%)
Congestion	4 (8%)	1 (2%)	3 (6%)	2 (4%)
Developmental malformation	1 (2%)	2 (4%)	1 (2%)	
Eosinophilic focus	19 (38%)	24 (48%)	22 (44%)	15 (30%)
Fibrosis	1 (2%)	1 (2%)		
Hematopoietic cell proliferation		1 (2%)	1 (2%)	2 (4%)
Hemorrhage		1 (2%)	1 (2%)	
Hepatodiaphragmatic nodule	9 (18%)	8 (16%)	3 (6%)	3 (6%)
Inflammation, chronic active	9 (18%)	1 (2%)	2 (4%)	4 (8%)
Mitotic alteration	1 (2%)			1 (2%)
Mixed cell focus	2 (4%)	4 (8%)	1 (2%)	5 (10%)
Necrosis	6 (12%)	1 (2%)	1 (2%)	
Pigmentation	6 (12%)	2 (4%)	6 (12%)	17 (34%)
Tension lipidosis	3 (6%)	1 (2%)		
Vacuolization cytoplasmic	10 (20%)	7 (14%)	9 (18%)	18 (36%)
Bile duct, hyperplasia	20 (40%)	29 (58%)	34 (68%)	29 (58%)
Capsule, inflammation, chronic				2 (4%)
Centrilobular, cytomegaly		1 (2%)	4 (8%)	20 (40%)
Centrilobular, degeneration	1 (2%)	2 (4%)	2 (4%)	7 (14%)
Centrilobular, necrosis	1 (2%)	2 (4%)	1 (2%)	

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Alimentary System (continued)				
Mesentery	(9)	(11)	(7)	(12)
Ectopic spleen			1 (14%)	
Inflammation				1 (8%)
Fat, necrosis	8 (89%)	9 (82%)	6 (86%)	11 (92%)
Oral mucosa	(2)	(1)		(2)
Pharyngeal, hyperplasia				1 (50%)
Pharyngeal, inflammation, acute		1 (100%)		
Pancreas	(49)	(50)	(50)	(50)
Atrophy	22 (45%)	14 (28%)	13 (26%)	14 (28%)
Cytoplasmic alteration	1 (2%)			
Ectopic liver		2 (4%)	2 (4%)	3 (6%)
Hyperplasia		3 (6%)	2 (4%)	
Inflammation, chronic			1 (2%)	2 (4%)
Salivary glands	(50)	(50)	(50)	(50)
Atrophy		2 (4%)	3 (6%)	1 (2%)
Cytoplasmic alteration		1 (2%)		1 (2%)
Inflammation, chronic		2 (4%)		
Stomach, forestomach	(50)	(50)	(50)	(50)
Fibrosis			1 (2%)	
Hyperkeratosis	1 (2%)			
Inflammation, acute	1 (2%)		1 (2%)	
Inflammation, chronic			1 (2%)	1 (2%)
Inflammation, chronic active	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Ulcer	3 (6%)	3 (6%)	4 (8%)	4 (8%)
Epithelium, hyperplasia, squamous	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Erosion	6 (12%)	9 (18%)	9 (18%)	7 (14%)
Inflammation, chronic				1 (2%)
Inflammation, chronic active	1 (2%)			
Mineralization			2 (4%)	
Ulcer	1 (2%)	1 (2%)	3 (6%)	
Tongue			(1)	(2)
Epithelium, hyperplasia			1 (100%)	1 (50%)
Cardiovascular System				
Heart	(49)	(50)	(50)	(50)
Cardiomyopathy	42 (86%)	43 (86%)	43 (86%)	36 (72%)
Inflammation, chronic active	1 (2%)			
Mineralization	1 (2%)			
Thrombosis			2 (4%)	1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)			
Atrophy			1 (2%)	
Congestion		1 (2%)		1 (2%)
Cyst		1 (2%)		1 (2%)
Hematopoietic cell proliferation	1 (2%)			
Hemorrhage	1 (2%)			
Hyperplasia	11 (22%)	12 (24%)	9 (18%)	6 (12%)
Vacuolization cytoplasmic	6 (12%)	8 (16%)	6 (12%)	3 (6%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Endocrine System (continued)				
Adrenal medulla	(50)	(50)	(50)	(49)
Hyperplasia	5 (10%)	7 (14%)	8 (16%)	2 (4%)
Necrosis		1 (2%)		
Islets, pancreatic	(49)	(50)	(50)	(50)
Hyperplasia			1 (2%)	1 (2%)
Parathyroid gland	(48)	(50)	(48)	(50)
Hyperplasia	1 (2%)			
Pituitary gland	(49)	(50)	(50)	(50)
Pigmentation			1 (2%)	
Pars distalis, angiectasis	11 (22%)	9 (18%)	12 (24%)	4 (8%)
Pars distalis, cyst	16 (33%)	18 (36%)	20 (40%)	8 (16%)
Pars distalis, ectasia		1 (2%)		
Pars distalis, hemorrhage	1 (2%)			
Pars distalis, hyperplasia	22 (45%)	29 (58%)	21 (42%)	18 (36%)
Pars intermedia, hyperplasia	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
Ultimobranchial cyst		3 (6%)		1 (2%)
C-cell, hyperplasia	16 (32%)	17 (34%)	13 (26%)	10 (20%)
Follicular cell, hyperplasia	1 (2%)			
General Body System				
None				
Genital System				
Clitoral gland	(47)	(48)	(50)	(49)
Hyperplasia	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Inflammation, acute	1 (2%)	2 (4%)		
Inflammation, chronic	3 (6%)	1 (2%)	5 (10%)	2 (4%)
Inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Vacuolization cytoplasmic				1 (2%)
Bilateral, inflammation, acute			1 (2%)	
Duct, ectasia	3 (6%)	5 (10%)	4 (8%)	2 (4%)
Ovary	(50)	(50)	(50)	(50)
Congestion	1 (2%)			
Cyst	3 (6%)	7 (14%)	4 (8%)	2 (4%)
Hyperplasia		1 (2%)		
Inflammation, chronic	1 (2%)			1 (2%)
Pigmentation			1 (2%)	
Bilateral, cyst		1 (2%)		2 (4%)
Uterus	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)		
Cyst		1 (2%)		1 (2%)
Developmental malformation			1 (2%)	
Dilatation		1 (2%)	1 (2%)	2 (4%)
Hemorrhage		1 (2%)		1 (2%)
Hyperplasia				1 (2%)
Hyperplasia, cystic	6 (12%)		5 (10%)	7 (14%)
Inflammation, acute				1 (2%)
Inflammation, chronic		1 (2%)		1 (2%)
Inflammation, chronic active		1 (2%)		
Metaplasia, squamous			1 (2%)	
Necrosis	1 (2%)			1 (2%)
Cervix, hypertrophy			1 (2%)	
Cervix, inflammation, chronic				1 (2%)

TABLE B5

Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Depletion cellular	1 (2%)		2 (4%)	2 (4%)
Fibrosis	1 (2%)	1 (2%)		
Hyperplasia	3 (6%)	4 (8%)		1 (2%)
Hyperplasia, reticulum cell		1 (2%)		
Necrosis			1 (2%)	
Erythroid cell, hyperplasia			1 (2%)	
Myeloid cell, hyperplasia		1 (2%)		
Lymph node	(7)	(9)	(15)	(19)
Iliac, congestion	2 (29%)			
Iliac, ectasia				2 (11%)
Mediastinal, congestion	3 (43%)	1 (11%)	4 (27%)	1 (5%)
Mediastinal, hyperplasia, lymphoid			1 (7%)	
Mediastinal, pigmentation	1 (14%)			1 (5%)
Pancreatic, congestion			1 (7%)	
Pancreatic, pigmentation		1 (11%)		
Renal, congestion	1 (14%)	1 (11%)	1 (7%)	
Renal, ectasia		1 (11%)		1 (5%)
Renal, hyperplasia, lymphoid				1 (5%)
Lymph node, mandibular	(49)	(50)	(50)	(50)
Atrophy	1 (2%)			
Congestion		1 (2%)	1 (2%)	
Ectasia	3 (6%)	4 (8%)	9 (18%)	2 (4%)
Edema				1 (2%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		1 (2%)
Hyperplasia, plasma cell	1 (2%)			
Infiltration cellular, plasma cell		1 (2%)		
Necrosis			1 (2%)	
Lymph node, mesenteric	(49)	(50)	(50)	(50)
Congestion	2 (4%)		3 (6%)	
Ectasia			4 (8%)	
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid		2 (4%)		2 (4%)
Inflammation, acute				1 (2%)
Inflammation, chronic				1 (2%)
Spleen	(50)	(50)	(50)	(50)
Atrophy				1 (2%)
Congestion	1 (2%)		2 (4%)	
Fibrosis	2 (4%)	3 (6%)	3 (6%)	4 (8%)
Hematopoietic cell proliferation	2 (4%)	4 (8%)		2 (4%)
Hemorrhage		2 (4%)		
Metaplasia, osseous		1 (2%)		
Necrosis		1 (2%)	2 (4%)	1 (2%)
Pigmentation				1 (2%)
Capsule, inflammation, chronic				1 (2%)
Thymus	(50)	(50)	(50)	(50)
Congestion			1 (2%)	
Cyst			1 (2%)	
Ectopic parathyroid gland	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Fibrosis		1 (2%)		
Inflammation, acute	1 (2%)			
Inflammation, chronic				1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Galactocoele	3 (6%)	5 (10%)	1 (2%)	
Hyperplasia	5 (10%)	2 (4%)	6 (12%)	5 (10%)
Inflammation, chronic active			1 (2%)	
Duct, dilatation	13 (26%)	9 (18%)	13 (26%)	13 (26%)
Skin	(50)	(50)	(50)	(50)
Hyperkeratosis			2 (4%)	
Hyperplasia, squamous	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute	1 (2%)			1 (2%)
Inflammation, chronic	1 (2%)			
Inflammation, chronic active	2 (4%)	1 (2%)		1 (2%)
Subcutaneous tissue, fibrosis		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteopetrosis	9 (18%)	12 (24%)	10 (20%)	5 (10%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)		2 (4%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)			
Hemorrhage				1 (2%)
Infiltration cellular, histiocyte	13 (26%)	10 (20%)	9 (18%)	11 (22%)
Inflammation, chronic	9 (18%)	8 (16%)	6 (12%)	8 (16%)
Bronchiole, alveolus, hyperplasia			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Congestion			1 (2%)	
Cyst	1 (2%)	1 (2%)		
Hemorrhage				1 (2%)
Inflammation, chronic	2 (4%)		3 (6%)	
Inflammation, chronic active	15 (30%)	15 (30%)	16 (32%)	19 (38%)
Nasolacrimal duct, cyst		2 (4%)		
Nasolacrimal duct, inflammation, chronic active	1 (2%)		1 (2%)	
Respiratory epithelium, hyperplasia				1 (2%)
Special Senses System				
Eye			(1)	(2)
Hemorrhage			1 (100%)	2 (100%)
Harderian gland	(1)			
Inflammation, chronic	1 (100%)			

TABLE B5**Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine**

	0 ppm	100 ppm	200 ppm	400 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet				1 (2%)
Congestion	2 (4%)		1 (2%)	
Cyst			1 (2%)	
Hydronephrosis		2 (4%)		
Inflammation, acute				1 (2%)
Mineralization	3 (6%)		4 (8%)	6 (12%)
Nephropathy	41 (82%)	42 (84%)	35 (70%)	37 (74%)
Pigmentation			2 (4%)	1 (2%)
Renal tubule, hyperplasia				1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Inflammation, chronic		3 (6%)	1 (2%)	2 (4%)

APPENDIX C **SUMMARY OF LESIONS IN MALE WISTAR RATS** **IN THE 2-YEAR DRINKING WATER STUDY** **OF PYRIDINE**

TABLE C1	Summary of the Incidence of Neoplasms in Male Wistar Rats	
	in the 2-Year Drinking Water Study of Pyridine	C-2
TABLE C2	Individual Animal Tumor Pathology of Male Wistar Rats	
	in the 2-Year Drinking Water Study of Pyridine	C-6
TABLE C3	Statistical Analysis of Primary Neoplasms in Male Wistar Rats	
	in the 2-Year Drinking Water Study of Pyridine	C-28
TABLE C4	Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats	
	in the 2-Year Drinking Water Study of Pyridine	C-32

TABLE C1
Summary of the Incidence of Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine^a

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	2	9	9	10
Natural deaths	26	27	30	33
Survivors				
Terminal sacrifice	22	14	11	7
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(32)	(37)	(29)	(27)
Carcinoma	1 (3%)			
Intestine small, duodenum	(39)	(44)	(42)	(42)
Carcinoma		1 (2%)		
Intestine small, jejunum	(37)	(36)	(34)	(35)
Carcinoma	1 (3%)	2 (6%)		
Intestine small, ileum	(28)	(32)	(28)	(31)
Liver	(50)	(50)	(50)	(50)
Cholangiocarcinoma	1 (2%)			2 (4%)
Hepatocellular adenoma	2 (4%)		1 (2%)	
Histiocytic sarcoma				1 (2%)
Oral mucosa	(5)	(1)	(1)	
Squamous cell carcinoma	1 (20%)			
Pancreas	(46)	(50)	(50)	(49)
Carcinoma		1 (2%)		
Acinus, adenoma	6 (13%)	7 (14%)	8 (16%)	7 (14%)
Acinus, adenoma, multiple	8 (17%)	4 (8%)	4 (8%)	
Acinus, carcinoma	2 (4%)		2 (4%)	
Acinus, carcinoma, multiple	2 (4%)		1 (2%)	
Stomach, forestomach	(49)	(50)	(50)	(49)
Fibrosarcoma			1 (2%)	
Squamous cell papilloma				1 (2%)
Stomach, glandular	(49)	(50)	(48)	(48)
Fibrosarcoma, metastatic, stomach, forestomach			1 (2%)	
Tongue			(1)	
Squamous cell carcinoma			1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocardium, schwannoma benign	2 (4%)	2 (4%)		1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Carcinoma				1 (2%)
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Pheochromocytoma benign	5 (10%)	4 (8%)	1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Endocrine System (continued)				
Islets, pancreatic	(47)	(50)	(49)	(49)
Adenoma	8 (17%)		3 (6%)	
Carcinoma		1 (2%)		1 (2%)
Parathyroid gland	(48)	(47)	(48)	(47)
Adenoma	1 (2%)			
Pituitary gland	(49)	(49)	(50)	(50)
Pars distalis, adenoma	15 (31%)	16 (33%)	12 (24%)	13 (26%)
Pars distalis, adenoma, multiple	1 (2%)	1 (2%)		
Pars intermedia, adenoma	1 (2%)			1 (2%)
Thyroid gland	(49)	(50)	(48)	(49)
Bilateral, follicular cell, adenoma			1 (2%)	
C-cell, adenoma	4 (8%)	2 (4%)		3 (6%)
Follicular cell, adenoma			4 (8%)	
Follicular cell, carcinoma	3 (6%)	3 (6%)	1 (2%)	
General Body System				
Tissue NOS		(1)		
Hemangiosarcoma		1 (100%)		
Genital System				
Epididymis	(50)	(49)	(49)	(50)
Preputial gland	(50)	(48)	(50)	(50)
Adenoma	1 (2%)		1 (2%)	1 (2%)
Prostate	(50)	(49)	(50)	(50)
Adenoma	3 (6%)	1 (2%)	1 (2%)	
Schwannoma malignant				1 (2%)
Seminal vesicle	(49)	(49)	(50)	(49)
Testes	(50)	(49)	(49)	(50)
Bilateral, interstitial cell, adenoma	3 (6%)	1 (2%)	1 (2%)	5 (10%)
Interstitial cell, adenoma	2 (4%)	5 (10%)	3 (6%)	7 (14%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Lymph node	(31)	(44)	(38)	(32)
Iliac, hemangiosarcoma		1 (2%)		
Pancreatic, histiocytic sarcoma				1 (3%)
Lymph node, mandibular	(48)	(49)	(47)	(48)
Histiocytic sarcoma				1 (2%)
Lymph node, mesenteric	(46)	(50)	(50)	(50)
Hemangioma				1 (2%)
Hemangiosarcoma		1 (2%)	1 (2%)	
Histiocytic sarcoma				1 (2%)
Spleen	(49)	(50)	(49)	(49)
Hemangiosarcoma		1 (2%)		
Thymus	(48)	(49)	(49)	(50)
Thymoma benign	1 (2%)		2 (4%)	
Thymoma malignant	1 (2%)			

TABLE C1
Summary of the Incidence of Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Integumentary System				
Mammary gland	(48)	(46)	(44)	(46)
Carcinoma			1 (2%)	
Fibroadenoma	1 (2%)	1 (2%)		1 (2%)
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma		1 (2%)		
Basal cell carcinoma				1 (2%)
Carcinoma, metastatic, Zymbal's gland			1 (2%)	
Fibroma			2 (4%)	
Keratoacanthoma	7 (14%)	3 (6%)	2 (4%)	1 (2%)
Squamous cell carcinoma		1 (2%)		
Squamous cell papilloma	2 (4%)	1 (2%)	1 (2%)	
Sebaceous gland, adenoma			1 (2%)	
Subcutaneous tissue, fibroma	5 (10%)	6 (12%)		1 (2%)
Subcutaneous tissue, fibroma, multiple				1 (2%)
Subcutaneous tissue, fibrosarcoma			1 (2%)	1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cranium, osteoma	1 (2%)			
Joint, sarcoma				1 (2%)
Skeletal muscle	(1)		(2)	
Fibroma			1 (50%)	
Lipoma	1 (100%)		1 (50%)	
Nervous System				
Brain	(50)	(49)	(50)	(50)
Astrocytoma malignant	1 (2%)	1 (2%)	1 (2%)	
Hemangioma	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma			1 (2%)	
Carcinoma, metastatic, Zymbal's gland			1 (2%)	1 (2%)
Fibrosarcoma, metastatic, skin				1 (2%)
Histiocytic sarcoma				1 (2%)
Nose	(50)	(50)	(50)	(50)
Chondroma				1 (2%)
Squamous cell carcinoma, metastatic, oral mucosa	1 (2%)			
Special Senses System				
Zymbal's gland	(1)		(2)	(3)
Carcinoma	1 (100%)		2 (100%)	3 (100%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Histiocytic sarcoma				1 (2%)
Lipoma	1 (2%)			
Renal tubule, adenoma	1 (2%)	4 (8%)	1 (2%)	2 (4%)
Renal tubule, adenoma, multiple	1 (2%)	1 (2%)		
Renal tubule, carcinoma				1 (2%)
Systemic Lesions				
Multiple organs ^b	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	1 (2%)	1 (2%)	2 (4%)	
Lymphoma malignant		2 (4%)		1 (2%)
Mesothelioma malignant			1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms ^c	43	38	32	39
Total primary neoplasms	101	79	68	62
Total animals with benign neoplasms	40	37	29	33
Total benign neoplasms	84	61	51	47
Total animals with malignant neoplasms	17	14	12	13
Total malignant neoplasms	17	18	17	15
Total animals with metastatic neoplasms	1		3	2
Total metastatic neoplasms	1		4	2

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	2	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	7		
	8	6	3	5	5	7	7	8	8	9	9	0	1	1	2	3	4	4	5	6	7	7	8	9	0	
	3	8	6	7	9	2	6	7	9	2	8	1	6	8	4	9	4	4	4	0	4	6	1	5	1	
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	3	1	5	0	4	4	3	4	0	3	2	1	2	3	4	3	2	4	0	2	4	0	3	3	2	
	6	3	0	3	7	1	1	3	1	8	8	4	4	2	6	0	3	8	5	7	4	7	9	5	6	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, colon	A	+	A	A	A	+	+	A	+	+	+	A	A	+	+	A	A	A	A	+	+	+	+	A	+	
Intestine large, rectum	A	+	+	A	+	+	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	A	+	A	A	A	A	+	A	+	A	+	A	A	+	A	A	A	A	A	+	+	+	+	A	+	
Carcinoma																										
Intestine small, duodenum	A	+	+	A	A	+	+	A	+	+	+	A	A	+	+	+	A	A	+	+	+	+	+	A	+	
Intestine small, jejunum	A	+	+	A	A	+	+	+	+	+	+	A	A	A	+	A	A	A	+	+	+	+	+	A	+	
Carcinoma																										
Intestine small, ileum	A	+	+	A	A	A	+	A	A	A	A	A	A	A	+	A	A	A	A	A	A	+	A	A	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Cholangiocarcinoma																										
Hepatocellular adenoma																			X							
Mesentery		+											+											+	+	
Oral mucosa										+									+						+	
Squamous cell carcinoma										X																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	
Acinus, adenoma																										
Acinus, adenoma, multiple										X																
Acinus, carcinoma																										
Acinus, carcinoma, multiple																										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	
Stomach, forestomach	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	
Tooth																										
Cardiovascular System																										
Blood vessel		+		+	+		+					+		+										+		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Endocardium, schwannoma benign																										
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pheochromocytoma malignant										X																
Pheochromocytoma benign																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	
Adenoma																X					X					
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	
Adenoma																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	
Pars distalis, adenoma		X			X										X				X		X	X	X			
Pars distalis, adenoma, multiple																										
Pars intermedia, adenoma																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
C-cell, adenoma																									X	
Follicular cell, carcinoma																					X					

+: Tissue examined microscopically
A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7			
	0	0	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
	5	7	7	7	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total Tissues/ Tumors		
	2	2	1	0	0	0	0	0	1	1	1	1	1	1	1	2	2	2	3	3	3	4	4	4		4	
	5	1	9	2	4	6	8	9	0	1	2	5	6	7	8	0	2	9	3	4	7	0	2	5		9	
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Intestine large, colon	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35		
Intestine large, rectum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42		
Intestine large, cecum	A	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	32		
Carcinoma																				X					1		
Intestine small, duodenum	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39		
Intestine small, jejunum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37		
Carcinoma									X																1		
Intestine small, ileum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	28		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Cholangiocarcinoma																			X						1		
Hepatocellular adenoma																X									2		
Mesentery			+	+																			+		7		
Oral mucosa								+					+												5		
Squamous cell carcinoma																									1		
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46		
Acinus, adenoma							X						X	X		X			X	X					6		
Acinus, adenoma, multiple						X		X		X		X								X		X			8		
Acinus, carcinoma							X																	X	2		
Acinus, carcinoma, multiple															X							X			2		
Salivary glands	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48		
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Tooth																+				+					2		
Cardiovascular System																											
Blood vessel				+																					8		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Endocardium, schwannoma benign																		X						X	2		
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Pheochromocytoma malignant																									1		
Pheochromocytoma benign							X	X		X						X				X					5		
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47		
Adenoma			X			X	X				X				X		X								8		
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48		
Adenoma														X											1		
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Pars distalis, adenoma					X	X	X		X	X				X			X			X					15		
Pars distalis, adenoma, multiple																				X					1		
Pars intermedia, adenoma											X														1		
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
C-cell, adenoma					X												X					X			4		
Follicular cell, carcinoma	X																			X					3		

TABLE C2

[illegible]

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7		
Number of Days on Study	0	0	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	5	7	7	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total	
Carcass ID Number	2	2	1	0	0	0	0	0	1	1	1	1	1	1	1	2	2	2	3	3	3	4	4	4	4	Tissues/ Tumors	
	5	1	9	2	4	6	8	9	0	1	2	5	6	7	8	0	2	9	3	4	7	0	2	5	9		
General Body System																											
None																											
Genital System																											
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenoma															X											1	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenoma				X										X					X			+	+	+	+	3	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Bilateral, interstitial cell, adenoma			X			X				X																3	
Interstitial cell, adenoma																								X		2	
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	31	
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46	
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Thymoma benign						X																				1	
Thymoma malignant																										1	
Integumentary System																											
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48	
Fibroadenoma																		X								1	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Keratoacanthoma				X								X	X				X				X					7	
Squamous cell papilloma						X															X					2	
Subcutaneous tissue, fibroma					X							X					X									5	
Subcutaneous tissue, sarcoma																										1	
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Cranium, osteoma																										1	
Skeletal muscle															+											1	
Lipoma															X											1	
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Astrocytoma malignant																										1	
Hemangioma	X																									1	
Peripheral nerve											+															1	
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Squamous cell carcinoma, metastatic, oral mucosa																										1	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	

TABLE C2

Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	2	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	7			
	8	6	3	5	5	7	7	8	8	9	9	0	1	1	2	3	4	4	5	6	7	7	8	9	0		
	3	8	6	7	9	2	6	7	9	2	8	1	6	8	4	9	4	4	4	0	4	6	1	5	1		
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
	3	1	5	0	4	4	3	4	0	3	2	1	2	3	4	3	2	4	0	2	4	0	3	3	2		
	6	3	0	3	7	1	1	3	1	8	8	4	4	2	6	0	3	8	5	7	4	7	9	5	6		
Special Senses System																											
Ear	+																										
Harderian gland																											
Zymbal's gland	+																										
Carcinoma	X																										
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lipoma																											
Renal tubule, adenoma																											
Renal tubule, adenoma, multiple	X																										
Urinary bladder	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Leukemia mononuclear																											

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

TABLE C2

Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

Number of Days on Study	3	3	3	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6
	3	5	7	4	7	7	8	0	3	4	4	5	6	7	8	9	9	1	1	3	3	3	4	4	4	4
	6	2	2	5	0	9	6	6	6	1	9	2	1	3	1	3	5	0	1	4	8	9	2	7	9	9
Carcass ID Number	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	8	8	6	7	9	8	5	0	7	5	9	9	8	6	7	6	7	8	7	6	5	5	5	9	5	5
	0	2	3	7	6	1	8	0	8	3	2	8	8	0	9	5	0	5	2	4	7	4	2	9	1	1
Genital System (continued)																										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																										
Interstitial cell, adenoma																										
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, hemangiosarcoma																										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																										
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																										
Keratoacanthoma																										
Squamous cell carcinoma																										
Squamous cell papilloma																										
Subcutaneous tissue, fibroma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																										
Peripheral nerve																										
Spinal cord																										
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																										
Renal tubule, adenoma, multiple																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																										
Lymphoma malignant																										

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

[illegible]

TABLE C2

Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	3	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6
	5	0	4	7	7	8	8	8	9	0	0	1	1	2	4	6	7	8	0	2	2	3	3	3	4
	4	4	7	3	9	1	6	7	4	0	1	0	5	0	8	1	5	8	8	2	8	0	1	2	5
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	1	1	2	4	4	4	0	0	3	3	1	3	2	0	2	3	3	3	1	2	1	4	4	0	5
	3	4	9	9	7	4	7	3	2	0	9	1	7	8	4	7	3	8	5	3	2	5	6	6	0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	A	A	+	+	+	A	+	+	A	A	+	+	A	A	+	+	A	A	+
Intestine large, rectum	+	+	+	+	+	+	A	A	+	+	+	A	+	+	+	+	+	+	A	+	+	+	A	+	+
Intestine large, cecum	+	+	+	+	+	+	A	A	+	+	+	A	+	+	A	A	+	A	A	A	+	+	A	A	A
Intestine small, duodenum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	A	+	A	+	+	A	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	A	A	A	A	+	A	A	+	+
Intestine small, ileum	+	+	A	+	+	+	A	A	+	+	+	A	+	+	A	A	A	+	A	A	A	A	A	A	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery																									
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma							X					X						X						X	
Acinus, adenoma, multiple																						X			
Acinus, carcinoma																									
Acinus, carcinoma, multiple																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Fibrosarcoma, metastatic, stomach, forestomach																									
Tongue																									
Squamous cell carcinoma																									
Tooth	+																							+	
Cardiovascular System																									
Blood vessel	+						+			+	+	+							+	+	+	+			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant							X																		
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Adenoma												X													
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X				X											X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Bilateral, follicular cell, adenoma																									
Follicular cell, adenoma																						X			
Follicular cell, carcinoma																								X	
General Body System																									
None																									
Genital System																									
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7			
	5	6	6	7	7	8	8	8	0	0	0	0	1	2	2	2	2	2	2	2	2	2	2	2			
	0	0	4	4	4	5	2	3	8	0	4	4	5	3	1	2	2	2	2	2	2	2	2	2			
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1			
	0	4	4	1	4	2	0	4	1	2	3	3	2	2	0	0	0	1	1	1	2	2	3	3			
	1	1	8	8	3	0	9	2	1	2	5	6	8	1	2	4	5	0	6	7	5	6	4	9			
																											Total Tissues/Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Intestine large, colon	A	A	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36		
Intestine large, rectum	A	A	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41		
Intestine large, cecum	A	A	A	A	A	A	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	M	+	29		
Intestine small, duodenum	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	42		
Intestine small, jejunum	+	+	A	+	A	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	34		
Intestine small, ileum	A	+	A	A	A	A	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	28		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Hepatocellular adenoma															X										1		
Mesentery								+									+								2		
Oral mucosa										+															1		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Acinus, adenoma	X												X		X		X								8		
Acinus, adenoma, multiple															X					X	X				4		
Acinus, carcinoma																X						X			2		
Acinus, carcinoma, multiple															X										1		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47		
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Fibrosarcoma								X																	1		
Stomach, glandular	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48		
Fibrosarcoma, metastatic, stomach, forestomach								X																	1		
Tongue													+												1		
Squamous cell carcinoma												X													1		
Tooth												+								+					4		
Cardiovascular System																											

Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

[illegible]

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

[illegible]

TABLE C2

Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	3	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6
	5	0	4	7	7	8	8	8	9	0	0	1	1	2	4	6	7	8	0	2	2	3	3	3	4	4
	4	4	7	3	9	1	6	7	4	0	1	0	5	0	8	1	5	8	8	2	8	0	1	2	5	5
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	1	1	2	4	4	4	0	0	3	3	1	3	2	0	2	3	3	3	1	2	1	4	4	0	5	5
	3	4	9	9	7	4	7	3	2	0	9	1	7	8	4	7	3	8	5	3	2	5	6	6	0	0
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																										
Renal tubule, adenoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																										
Mesothelioma malignant																										

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7		
Number of Days on Study	5	6	6	7	7	8	8	8	0	0	0	0	1	2	2	2	2	2	2	2	2	2	2	2		
	0	0	4	4	5	2	3	8	0	4	4	5	3	1	2	2	2	2	2	2	2	2	2	2		
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Total	
	0	4	4	1	4	2	0	4	1	2	3	3	2	2	0	0	0	1	1	1	2	2	3	3	4	Tissues/ Tumors
	1	1	8	8	3	0	9	2	1	2	5	6	8	1	2	4	5	0	6	7	5	6	4	9	0	
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Alveolar/bronchiolar carcinoma, metastatic, lung												X													1	
Renal tubule, adenoma															X										1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	47	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leukemia mononuclear				X									X												2	
Mesothelioma malignant															X										1	

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

[illegible]

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7
	7	8	8	8	9	0	1	2	2	3	5	6	7	8	8	8	8	0	2	2	2	2	2	2	2	2
	4	0	2	7	5	6	6	7	9	1	8	0	4	2	3	5	7	9	2	2	2	2	2	2	2	2
Carcass ID Number	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	0	9	9	5	5	7	9	8	7	9	9	6	6	8	6	7	5	5	5	5	6	6	7	9		Total
	0	3	4	2	7	9	7	6	5	5	0	1	2	3	7	8	4	1	3	5	6	0	7	3	8	Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	A	+	A	+	+	A	+	+	+	+	+	A	A	+	A	A	A	+	+	+	+	+	+	+	33
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	+	A	A	+	A	+	A	+	+	+	+	+	+	+	40
Intestine large, cecum	+	A	+	A	+	A	A	+	A	+	A	+	A	A	+	A	A	A	+	+	+	+	+	+	+	27
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	A	A	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	A	+	A	+	+	A	+	A	+	+	+	A	A	+	A	A	A	+	+	+	+	+	+	+	35
Intestine small, ileum	+	A	+	A	+	A	A	+	A	+	+	+	A	A	+	A	A	A	+	+	+	+	+	+	+	31
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																										2
Histiocytic sarcoma																										1
Mesentery											+															2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, adenoma											X								X		X	X				7
Salivary glands	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth								+										+				+				3
Cardiovascular System																										
Blood vessel						+																				3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocardium, schwannoma benign																		X								1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																		X								1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma											X															1
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma						X	X	X		X	X	X	X										X	X		13
Pars intermedia, adenoma																	X									1
Thyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma	X									X												X				3
General Body System																										
None																										
Genital System																										
Coagulating gland	+	+	+	+	+	+	A	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	45
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant													X													1
Seminal vesicle	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma				X														X					X	X		5
Interstitial cell, adenoma			X						X																X	7

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

	0	4	4	4	4	4	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	
Number of Days on Study	9	4	5	6	6	6	6	6	8	8	8	9	9	1	3	3	3	4	5	5	5	5	5	6	6	
	4	3	0	3	4	6	7	8	3	6	9	3	9	1	1	2	9	5	0	2	3	3	6	2	8	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Carcass ID Number	8	5	6	8	9	8	7	7	9	6	7	8	6	7	7	6	5	8	6	8	8	9	8	9	7	
	0	8	1	9	9	3	1	9	2	6	8	6	4	6	0	9	4	1	5	2	8	5	4	7	2	
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma																	X									
Lymph node	+				+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+			+	
Pancreatic, histiocytic sarcoma																		X								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	
Histiocytic sarcoma																		X								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangioma																										
Histiocytic sarcoma																		X								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Integumentary System																										
Mammary gland	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fibroadenoma																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Basal cell carcinoma																										
Keratoacanthoma																										
Subcutaneous tissue, fibroma																										
Subcutaneous tissue, fibroma, multiple																										
Subcutaneous tissue, fibrosarcoma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Joint, sarcoma																										
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Peripheral nerve					+												+									
Spinal cord																	+									
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Carcinoma, metastatic, Zymbal s gland																										
Fibrosarcoma, metastatic, skin																										
Histiocytic sarcoma																		X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Chondroma																										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Ear																		+								
Harderian gland																										
Zymbal s gland								+																		
Carcinoma								X																		

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7		
Number of Days on Study	7	8	8	8	9	0	1	2	2	3	5	6	7	8	8	8	8	0	2	2	2	2	2	2	2		
	4	0	2	7	5	6	6	7	9	1	8	0	4	2	3	5	7	9	2	2	2	2	2	2	2		
	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Total	
Carcass ID Number	0	9	9	5	5	5	7	9	8	7	9	9	6	6	8	6	7	5	5	5	5	6	6	7	9	Tissues/ Tumors	
	0	3	4	2	7	9	7	6	5	5	0	1	2	3	7	8	4	1	3	5	6	0	7	3	8		
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																										1	
Lymph node	+	+					+					+	+	+		+	+	+		+	+		+		+	32	
Pancreatic, histiocytic sarcoma																										1	
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Histiocytic sarcoma																										1	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hemangioma											X															1	
Histiocytic sarcoma																										1	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Integumentary System																											
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46	
Fibroadenoma										X																1	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Basal cell carcinoma																										1	
Keratoacanthoma																	X									1	
Subcutaneous tissue, fibroma																						X				1	
Subcutaneous tissue, fibroma, multiple																							X			1	
Subcutaneous tissue, fibrosarcoma																		X								1	
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Joint, sarcoma																						X				1	
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Peripheral nerve			+							+												+				5	
Spinal cord			+							+												+				4	
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	50	
Carcinoma, metastatic, Zymbal s gland																										1	
Fibrosarcoma, metastatic, skin																					X					1	
Histiocytic sarcoma																										1	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Chondroma			X																							1	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Special Senses System																											
Ear																										1	
Harderian gland															+											1	
Zymbal s gland															+		+									3	
Carcinoma															X		X									3	

Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Board Draft

TABLE C2

Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	
	7	8	8	8	9	0	1	2	2	3	5	6	7	8	8	8	8	0	2	2	2	2	2	2	2	2	
	4	0	2	7	5	6	6	7	9	1	8	0	4	2	3	5	7	9	2	2	2	2	2	2	2	2	
Carcass ID Number	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Total
	0	9	9	5	5	5	7	9	8	7	9	9	6	6	8	6	7	5	5	5	5	6	6	7	9	Tissues/	
	0	3	4	2	7	9	7	6	5	5	0	1	2	3	7	8	4	1	3	5	6	0	7	3	8	Tumors	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Renal tubule, adenoma							X								X												2
Renal tubule, carcinoma																X											1
Urinary bladder	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	44
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Lymphoma malignant																											1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate ^a	5/50 (10%)	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted rate ^b	12.5%	11.1%	3.0%	0.0%
Terminal rate ^c	5/22 (23%)	2/14 (14%)	0/11 (0%)	0/7 (0%)
First incidence (days)	722 (T)	486	721	^e
Poly-3 test ^d	P=0.022N	P=0.568N	P=0.144N	P=0.073N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	6/50 (12%)	5/50 (10%)	2/50 (4%)	1/50 (2%)
Adjusted rate	14.8%	13.8%	5.8%	3.5%
Terminal rate	5/22 (23%)	2/14 (14%)	0/11 (0%)	0/7 (0%)
First incidence (days)	587	486	481	553
Poly-3 test	P=0.055N	P=0.582N	P=0.189N	P=0.133N
Small Intestine (Duodenum, Jejunum): Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	2.5%	8.5%	0.0%	0.0%
Terminal rate	1/22 (5%)	2/14 (14%)	0/11 (0%)	0/7 (0%)
First incidence (days)	722 (T)	698		
Poly-3 test	P=0.221N	P=0.259	P=0.534N	P=0.569N
Kidney (Renal Tubule): Adenoma (Single Sections)				
Overall rate	2/50 (4%)	5/50 (10%)	1/50 (2%)	2/50 (4%)
Adjusted rate	4.9%	13.9%	3.0%	7.0%
Terminal rate	0/22 (0%)	1/14 (7%)	0/11 (0%)	0/7 (0%)
First incidence (days)	576	610	721	606
Poly-3 test	P=0.531N	P=0.167	P=0.564N	P=0.562
Kidney (Renal Tubule): Adenoma or Carcinoma (Single Sections)				
Overall rate	2/50 (4%)	5/50 (10%)	1/50 (2%)	3/50 (6%)
Adjusted rate	4.9%	13.9%	3.0%	10.4%
Terminal rate	0/22 (0%)	1/14 (7%)	0/11 (0%)	0/7 (0%)
First incidence (days)	576	610	721	606
Poly-3 test	P=0.420	P=0.167	P=0.564N	P=0.348
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	3/50 (6%)	6/50 (12%)	5/50 (10%)	4/50 (8%)
Adjusted rate	7.4%	16.5%	14.4%	13.6%
Terminal rate	1/22 (5%)	1/14 (7%)	2/11 (18%)	0/7 (0%)
First incidence (days)	576	610	520	550
Poly-3 test	P=0.288	P=0.187	P=0.271	P=0.328
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	3/50 (6%)	6/50 (12%)	6/50 (12%)	4/50 (8%)
Adjusted rate	7.4%	16.5%	17.2%	13.6%
Terminal rate	1/22 (5%)	1/14 (7%)	2/11 (18%)	0/7 (0%)
First incidence (days)	576	610	520	550
Poly-3 test	P=0.258	P=0.187	P=0.167	P=0.328
Pancreas: Adenoma				
Overall rate	14/46 (30%)	11/50 (22%)	12/50 (24%)	7/49 (14%)
Adjusted rate	37.4%	28.3%	32.9%	23.7%
Terminal rate	13/22 (59%)	4/14 (29%)	4/11 (36%)	3/7 (43%)
First incidence (days)	589	372	486	545
Poly-3 test	P=0.176N	P=0.267N	P=0.433N	P=0.168N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Pancreas: Carcinoma				
Overall rate	4/46 (9%)	1/50 (2%)	3/50 (6%)	0/49 (0%)
Adjusted rate	10.8%	2.8%	8.9%	0.0%
Terminal rate	4/22 (18%)	0/14 (0%)	3/11 (27%)	0/7 (0%)
First incidence (days)	722 (T)	638	722 (T)	
Poly-3 test	P=0.107N	P=0.190N	P=0.550N	P=0.105N
Pancreas: Adenoma or Carcinoma				
Overall rate	16/46 (35%)	11/50 (22%)	13/50 (26%)	7/49 (14%)
Adjusted rate	42.7%	28.3%	35.6%	23.7%
Terminal rate	15/22 (68%)	4/14 (29%)	5/11 (46%)	3/7 (43%)
First incidence (days)	589	372	486	545
Poly-3 test	P=0.098N	P=0.131N	P=0.343N	P=0.077N
Pancreatic Islets: Adenoma				
Overall rate	8/47 (17%)	0/50 (0%)	3/49 (6%)	0/49 (0%)
Adjusted rate	20.8%	0.0%	8.8%	0.0%
Terminal rate	5/22 (23%)	0/14 (0%)	0/11 (0%)	0/7 (0%)
First incidence (days)	624		510	
Poly-3 test	P=0.005N	P=0.005N	P=0.134N	P=0.014N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	8/47 (17%)	1/50 (2%)	3/49 (6%)	1/49 (2%)
Adjusted rate	20.8%	2.8%	8.8%	3.6%
Terminal rate	5/22 (23%)	0/14 (0%)	0/11 (0%)	0/7 (0%)
First incidence (days)	624	638	510	631
Poly-3 test	P=0.025N	P=0.020N	P=0.134N	P=0.048N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	16/49 (33%)	17/49 (35%)	12/50 (24%)	13/50 (26%)
Adjusted rate	38.2%	45.7%	33.1%	39.7%
Terminal rate	9/22 (41%)	5/14 (36%)	4/11 (36%)	2/7 (29%)
First incidence (days)	468	506	494	483
Poly-3 test	P=0.480N	P=0.324	P=0.404N	P=0.545
Prostate: Adenoma				
Overall rate	3/50 (6%)	1/49 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	7.5%	2.9%	3.0%	0.0%
Terminal rate	3/22 (14%)	1/14 (7%)	1/11 (9%)	0/7 (0%)
First incidence (days)	722 (T)	722 (T)	722 (T)	
Poly-3 test	P=0.097N	P=0.363N	P=0.368N	P=0.195N
Skin: Keratoacanthoma				
Overall rate	7/50 (14%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate	17.2%	8.5%	5.9%	3.5%
Terminal rate	4/22 (18%)	2/14 (14%)	1/11 (9%)	0/7 (0%)
First incidence (days)	598	639	705	687
Poly-3 test	P=0.035N	P=0.216N	P=0.128N	P=0.090N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	9/50 (18%)	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted rate	21.8%	11.3%	8.7%	3.5%
Terminal rate	5/22 (23%)	3/14 (21%)	1/11 (9%)	0/7 (0%)
First incidence (days)	576	639	548	687
Poly-3 test	P=0.014N	P=0.177N	P=0.106N	P=0.038N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma				
Overall rate	9/50 (18%)	5/50 (10%)	3/50 (6%)	1/50 (2%)
Adjusted rate	21.8%	14.1%	8.7%	3.5%
Terminal rate	5/22 (23%)	4/14 (29%)	1/11 (9%)	0/7 (0%)
First incidence (days)	576	639	548	687
Poly-3 test	P=0.013N	P=0.282N	P=0.106N	P=0.038N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma				
Overall rate	9/50 (18%)	6/50 (12%)	3/50 (6%)	2/50 (4%)
Adjusted rate	21.8%	17.0%	8.7%	7.1%
Terminal rate	5/22 (23%)	5/14 (36%)	1/11 (9%)	1/7 (14%)
First incidence (days)	576	639	548	687
Poly-3 test	P=0.036N	P=0.401N	P=0.106N	P=0.096N
Skin: Fibroma				
Overall rate	5/50 (10%)	6/50 (12%)	2/50 (4%)	2/50 (4%)
Adjusted rate	12.3%	16.7%	5.9%	7.1%
Terminal rate	3/22 (14%)	4/14 (29%)	1/11 (9%)	2/7 (29%)
First incidence (days)	572	552	683	722 (T)
Poly-3 test	P=0.198N	P=0.412	P=0.294N	P=0.388N
Skin: Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	6/50 (12%)	6/50 (12%)	3/50 (6%)	3/50 (6%)
Adjusted rate	14.6%	16.7%	8.8%	10.7%
Terminal rate	3/22 (14%)	4/14 (29%)	1/11 (9%)	2/7 (29%)
First incidence (days)	572	552	674	709
Poly-3 test	P=0.282N	P=0.527	P=0.338N	P=0.453N
Testes: Adenoma				
Overall rate	5/50 (10%)	6/49 (12%)	4/49 (8%)	12/50 (24%)
Adjusted rate	12.3%	16.9%	11.9%	36.6%
Terminal rate	3/22 (14%)	3/14 (21%)	1/11 (9%)	3/7 (43%)
First incidence (days)	592	486	660	464
Poly-3 test	P=0.008	P=0.404	P=0.618N	P=0.012
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/49 (8%)	2/50 (4%)	0/48 (0%)	3/49 (6%)
Adjusted rate	10.2%	5.6%	0.0%	10.6%
Terminal rate	3/22 (14%)	1/14 (7%)	0/11 (0%)	1/7 (14%)
First incidence (days)	701	581		574
Poly-3 test	P=0.483N	P=0.382N	P=0.085N	P=0.634
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	0/49 (0%)	0/50 (0%)	5/48 (10%)	0/49 (0%)
Adjusted rate	0.0%	0.0%	14.9%	0.0%
Terminal rate	0/22 (0%)	0/14 (0%)	1/11 (9%)	0/7 (0%)
First incidence (days)			630	
Poly-3 test	P=0.220		P=0.019	
Thyroid Gland (Follicular Cell): Carcinoma				
Overall rate	3/49 (6%)	3/50 (6%)	1/48 (2%)	0/49 (0%)
Adjusted rate	7.6%	8.4%	3.0%	0.0%
Terminal rate	1/22 (5%)	1/14 (7%)	0/11 (0%)	0/7 (0%)
First incidence (days)	674	593	645	
Poly-3 test	P=0.093N	P=0.618	P=0.370N	P=0.196N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	3/49 (6%)	3/50 (6%)	6/48 (13%)	0/49 (0%)
Adjusted rate	7.6%	8.4%	17.7%	0.0%
Terminal rate	1/22 (5%)	1/14 (7%)	1/11 (9%)	0/7 (0%)
First incidence (days)	674	593	630	
Poly-3 test	P=0.355N	P=0.618	P=0.168	P=0.196N
Zymbal's Gland: Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate	2.5%	0.0%	5.8%	10.3%
Terminal rate	0/22 (0%)	0/14 (0%)	0/11 (0%)	0/7 (0%)
First incidence (days)	660	494	466	
Poly-3 test	P=0.063	P=0.528N	P=0.447	P=0.200
All Organs: Hemangiosarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	0.0%	8.5%	3.0%	0.0%
Terminal rate	0/22 (0%)	2/14 (14%)	0/11 (0%)	0/7 (0%)
First incidence (days)		660	705	
Poly-3 test	P=0.519N	P=0.096	P=0.466	
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	2.5%	8.5%	3.0%	3.5%
Terminal rate	0/22 (0%)	2/14 (14%)	0/11 (0%)	0/7 (0%)
First incidence (days)		705	631	
Poly-3 test	P=0.573N	P=0.259	P=0.722	P=0.678
All Organs: Benign Neoplasms				
Overall rate	40/50 (80%)	37/50 (74%)	29/50 (58%)	33/50 (66%)
Adjusted rate	86.7%	84.4%	72.4%	81.9%
Terminal rate	21/22 (96%)	13/14 (93%)	8/11 (73%)	6/7 (86%)
First incidence (days)	468	372	486	464
Poly-3 test	P=0.214N	P=0.497N	P=0.055N	P=0.353N
All Organs: Malignant Neoplasms				
Overall rate	17/50 (34%)	14/50 (28%)	12/50 (24%)	13/50 (26%)
Adjusted rate	40.2%	37.5%	33.2%	40.5%
Terminal rate	9/22 (41%)	7/14 (50%)	3/11 (27%)	2/7 (29%)
First incidence (days)	587	552	481	466
Poly-3 test	P=0.513N	P=0.496N	P=0.341N	P=0.584
All Organs: Benign or Malignant Neoplasms				
Overall rate	43/50 (86%)	38/50 (76%)	32/50 (64%)	39/50 (78%)
Adjusted rate	91.2%	86.1%	78.4%	90.9%
Terminal rate	21/22 (96%)	13/14 (93%)	9/11 (82%)	7/7 (100%)
First incidence (days)	468	372	481	464
Poly-3 test	P=0.534N	P=0.306N	P=0.050N	P=0.656N

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, pancreas, pancreatic islets, pituitary gland, prostate gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by N.

^e Not applicable; no neoplasms in animal group

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine^a

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	2	9	9	10
Natural deaths	26	27	30	33
Survivors				
Terminal sacrifice	22	14	11	7
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Foreign body			1 (2%)	1 (2%)
Inflammation, acute				1 (2%)
Ulcer				1 (2%)
Muscularis, degeneration				1 (2%)
Intestine large, colon	(35)	(39)	(36)	(33)
Mineralization			1 (3%)	1 (3%)
Parasite metazoan			1 (3%)	
Intestine large, rectum	(42)	(42)	(41)	(40)
Hemorrhage	1 (2%)			
Mineralization		1 (2%)		
Parasite metazoan				1 (3%)
Ulcer				1 (3%)
Intestine large, cecum	(32)	(37)	(29)	(27)
Congestion			1 (3%)	
Edema		1 (3%)		
Hemorrhage	1 (3%)	2 (5%)	1 (3%)	
Inflammation, acute		2 (5%)	2 (7%)	1 (4%)
Inflammation, chronic			1 (3%)	1 (4%)
Ulcer		2 (5%)		2 (7%)
Artery, mineralization		1 (3%)		
Intestine small, jejunum	(37)	(36)	(34)	(35)
Inflammation, chronic				1 (3%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	5 (10%)	9 (18%)	2 (4%)	
Basophilic focus				2 (4%)
Cholangiofibrosis				1 (2%)
Clear cell focus	15 (30%)	7 (14%)	8 (16%)	8 (16%)
Congestion	19 (38%)	12 (24%)	6 (12%)	17 (34%)
Degeneration, cystic	7 (14%)	13 (26%)	9 (18%)	5 (10%)
Eosinophilic focus	14 (28%)	12 (24%)	4 (8%)	2 (4%)
Fibrosis	1 (2%)	5 (10%)	26 (52%)	31 (62%)
Hemorrhage	1 (2%)	1 (2%)	5 (10%)	3 (6%)
Hepatodiaphragmatic nodule	2 (4%)	1 (2%)	2 (4%)	
Hypertrophy			1 (2%)	
Infarct			1 (2%)	
Infiltration cellular, histiocyte		1 (2%)	2 (4%)	
Inflammation, acute	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Mineralization		1 (2%)	3 (6%)	3 (6%)
Mixed cell focus	1 (2%)		1 (2%)	1 (2%)
Necrosis	6 (12%)	7 (14%)	6 (12%)	2 (4%)

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Alimentary System (continued)				
Liver (continued)	(50)	(50)	(50)	(50)
Pigmentation	6 (12%)	15 (30%)	34 (68%)	42 (84%)
Regeneration				2 (4%)
Tension lipodosis			1 (2%)	
Thrombosis			1 (2%)	
Vacuolization cytoplasmic	18 (36%)	18 (36%)	12 (24%)	15 (30%)
Artery, mineralization		1 (2%)		
Bile duct, cyst			2 (4%)	3 (6%)
Bile duct, dilatation		2 (4%)		
Bile duct, hyperplasia	31 (62%)	33 (66%)	30 (60%)	27 (54%)
Centrilobular, cytomegaly		1 (2%)	1 (2%)	1 (2%)
Centrilobular, degeneration	1 (2%)	15 (30%)	25 (50%)	33 (66%)
Centrilobular, hypertrophy		1 (2%)		
Centrilobular, necrosis	5 (10%)	6 (12%)	4 (8%)	23 (46%)
Hepatocyte, atrophy	2 (4%)		1 (2%)	1 (2%)
Oval cell, hyperplasia	1 (2%)			
Periportal, fibrosis			5 (10%)	7 (14%)
Sinusoid, congestion	1 (2%)			
Mesentery	(7)	(1)	(2)	(2)
Mineralization	1 (14%)			
Artery, inflammation	5 (71%)	1 (100%)		1 (50%)
Artery, mineralization	2 (29%)			
Fat, necrosis	1 (14%)			1 (50%)
Vein, thrombosis			2 (100%)	
Oral mucosa	(5)	(1)	(1)	
Hyperplasia, squamous		1 (100%)	1 (100%)	
Inflammation, suppurative	3 (60%)			
Pancreas	(46)	(50)	(50)	(49)
Atrophy	2 (4%)	3 (6%)	3 (6%)	1 (2%)
Basophilic focus	1 (2%)			
Edema			1 (2%)	
Fibrosis			1 (2%)	
Hemorrhage		1 (2%)		
Hyperplasia	18 (39%)	18 (36%)	8 (16%)	8 (16%)
Necrosis	1 (2%)			
Acinus, hyperplasia	1 (2%)		1 (2%)	
Artery, inflammation	3 (7%)	5 (10%)	3 (6%)	
Artery, mineralization	2 (4%)	6 (12%)	1 (2%)	
Duct, hyperplasia	1 (2%)	1 (2%)	1 (2%)	
Salivary glands	(48)	(49)	(47)	(48)
Atrophy				1 (2%)
Inflammation, acute		1 (2%)		
Artery, mineralization	2 (4%)	3 (6%)		
Duct, cyst	1 (2%)		1 (2%)	
Stomach, forestomach	(49)	(50)	(50)	(49)
Cyst			1 (2%)	2 (4%)
Erosion	1 (2%)			
Fibrosis				1 (2%)
Foreign body			1 (2%)	2 (4%)
Hemorrhage			1 (2%)	
Hyperplasia, squamous	2 (4%)	13 (26%)	11 (22%)	10 (20%)
Inflammation, acute	1 (2%)			
Inflammation, chronic			1 (2%)	1 (2%)
Inflammation, chronic active				1 (2%)
Mineralization	3 (6%)	5 (10%)	3 (6%)	1 (2%)
Ulcer	2 (4%)	4 (8%)	3 (6%)	4 (8%)
Ulcer, chronic	1 (2%)			

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Alimentary System (continued)				
Stomach, glandular	(49)	(50)	(48)	(48)
Erosion	3 (6%)	3 (6%)	2 (4%)	4 (8%)
Fibrosis		1 (2%)		
Hemorrhage			2 (4%)	
Hyperplasia	1 (2%)		1 (2%)	
Inflammation, chronic active			1 (2%)	
Mineralization	8 (16%)	25 (50%)	16 (33%)	6 (13%)
Ulcer			1 (2%)	
Artery, mineralization			1 (2%)	1 (2%)
Serosa, edema		1 (2%)		
Tooth	(2)	(2)	(4)	(3)
Peridontal tissue, inflammation, chronic				1 (33%)
Peridontal tissue, inflammation, chronic active	1 (50%)			1 (33%)
Peridontal tissue, inflammation, granulomatous		1 (50%)		
Peridontal tissue, inflammation, suppurative	1 (50%)	1 (50%)	4 (100%)	1 (33%)
Cardiovascular System				
Blood vessel	(8)	(23)	(12)	(3)
Mineralization	6 (75%)	6 (26%)	1 (8%)	
Aorta, mineralization	7 (88%)	21 (91%)	10 (83%)	3 (100%)
Pulmonary artery, degeneration		1 (4%)		
Pulmonary artery, mineralization	3 (38%)	3 (13%)	5 (42%)	2 (67%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	49 (98%)	49 (98%)	49 (98%)	47 (94%)
Inflammation, chronic	1 (2%)			
Mineralization	6 (12%)	17 (34%)	12 (24%)	3 (6%)
Thrombosis	1 (2%)		1 (2%)	
Artery, inflammation		1 (2%)		
Artery, inflammation, acute				1 (2%)
Artery, mineralization	4 (8%)	15 (30%)	9 (18%)	2 (4%)
Artery, thrombosis	1 (2%)			
Atrium, dilatation			1 (2%)	1 (2%)
Atrium, thrombosis	4 (8%)	2 (4%)	5 (10%)	3 (6%)
Valve, inflammation				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)			
Angiectasis	1 (2%)		1 (2%)	
Congestion		2 (4%)		1 (2%)
Degeneration		2 (4%)		
Hemorrhage	3 (6%)			
Hyperplasia	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hypertrophy	2 (4%)	2 (4%)	2 (4%)	
Mineralization		1 (2%)		
Necrosis				2 (4%)
Thrombosis		1 (2%)		1 (2%)
Vacuolization cytoplasmic	17 (34%)	13 (26%)	12 (24%)	7 (14%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	3 (6%)	4 (8%)	2 (4%)	1 (2%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Endocrine System (continued)				
Islets, pancreatic	(47)	(50)	(49)	(49)
Hyperplasia	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Parathyroid gland	(48)	(47)	(48)	(47)
Hyperplasia	16 (33%)	32 (68%)	29 (60%)	12 (26%)
Inflammation, chronic	1 (2%)			
Pituitary gland	(49)	(49)	(50)	(50)
Angiectasis				1 (2%)
Congestion				2 (4%)
Cyst	17 (35%)	13 (27%)	18 (36%)	11 (22%)
Hemorrhage			1 (2%)	1 (2%)
Hyperplasia	13 (27%)	10 (20%)	7 (14%)	3 (6%)
Hypertrophy				1 (2%)
Pars distalis, hyperplasia	2 (4%)	1 (2%)		
Thyroid gland	(49)	(50)	(48)	(49)
Inflammation, granulomatous			1 (2%)	
C-cell, hyperplasia		1 (2%)	1 (2%)	
Follicle, cyst	2 (4%)	4 (8%)	5 (10%)	1 (2%)
Follicular cell, hyperplasia		2 (4%)	1 (2%)	
General Body System				
None				
Genital System				
Coagulating gland	(48)	(42)	(45)	(45)
Inflammation, acute		1 (2%)	1 (2%)	
Inflammation, chronic				1 (2%)
Inflammation, chronic active	1 (2%)			
Artery, mineralization		1 (2%)		
Epididymis	(50)	(49)	(49)	(50)
Arteriole, mineralization	1 (2%)			
Artery, inflammation				1 (2%)
Epithelium, hyperplasia				1 (2%)
Preputial gland	(50)	(48)	(50)	(50)
Atrophy			1 (2%)	
Hyperplasia, squamous				1 (2%)
Inflammation, chronic	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)	
Inflammation, suppurative	12 (24%)	9 (19%)	10 (20%)	3 (6%)
Duct, cyst	49 (98%)	43 (90%)	46 (92%)	48 (96%)
Prostate	(50)	(49)	(50)	(50)
Fibrosis			2 (4%)	1 (2%)
Hemorrhage	1 (2%)		1 (2%)	
Hyperplasia	4 (8%)	4 (8%)	1 (2%)	2 (4%)
Inflammation, acute	4 (8%)	1 (2%)		
Inflammation, chronic	3 (6%)	4 (8%)	5 (10%)	2 (4%)
Inflammation, chronic active	5 (10%)	5 (10%)	2 (4%)	2 (4%)
Artery, mineralization	1 (2%)			
Seminal vesicle	(49)	(49)	(50)	(49)
Cyst		1 (2%)		
Hyperplasia		1 (2%)		
Inflammation, chronic		1 (2%)		
Inflammation, chronic active			1 (2%)	
Artery, mineralization		1 (2%)		

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Genital System (continued)				
Testes	(50)	(49)	(49)	(50)
Atrophy	20 (40%)	20 (41%)	18 (37%)	9 (18%)
Congestion				1 (2%)
Inflammation, granulomatous			1 (2%)	1 (2%)
Mineralization	6 (12%)	2 (4%)	9 (18%)	4 (8%)
Artery, inflammation	24 (48%)	24 (49%)	14 (29%)	11 (22%)
Artery, mineralization		3 (6%)	2 (4%)	
Interstitial cell, hyperplasia	3 (6%)	4 (8%)	7 (14%)	7 (14%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		1 (2%)
Erythroid cell, hyperplasia		1 (2%)		
Myeloid cell, hyperplasia	2 (4%)	1 (2%)	1 (2%)	
Lymph node	(31)	(44)	(38)	(32)
Ectasia	2 (6%)	1 (2%)		
Hemorrhage	2 (6%)	1 (2%)		
Hyperplasia, plasma cell	2 (6%)			
Iliac, ectasia	5 (16%)	3 (7%)	3 (8%)	1 (3%)
Iliac, hemorrhage	1 (3%)	2 (5%)	2 (5%)	3 (9%)
Iliac, hyperplasia, lymphoid		1 (2%)	2 (5%)	1 (3%)
Iliac, hyperplasia, plasma cell		4 (9%)	2 (5%)	2 (6%)
Inguinal, atrophy	1 (3%)			
Inguinal, ectasia	1 (3%)		1 (3%)	
Inguinal, hemorrhage		1 (2%)	1 (3%)	1 (3%)
Inguinal, hyperplasia, lymphoid			1 (3%)	
Inguinal, infiltration cellular, histiocyte			1 (3%)	
Mediastinal, atrophy		1 (2%)		
Mediastinal, congestion	1 (3%)	3 (7%)	2 (5%)	1 (3%)
Mediastinal, ectasia	6 (19%)	12 (27%)	9 (24%)	6 (19%)
Mediastinal, hemorrhage	8 (26%)	15 (34%)	10 (26%)	9 (28%)
Mediastinal, hyperplasia, lymphoid				1 (3%)
Mediastinal, hyperplasia, plasma cell		2 (5%)	1 (3%)	1 (3%)
Pancreatic, ectasia	2 (6%)	5 (11%)		1 (3%)
Pancreatic, hemorrhage	4 (13%)	5 (11%)	4 (11%)	7 (22%)
Pancreatic, hyperplasia, lymphoid	2 (6%)	1 (2%)		4 (13%)
Pancreatic, hyperplasia, plasma cell	1 (3%)		2 (5%)	2 (6%)
Pancreatic, pigmentation			1 (3%)	
Renal, ectasia	15 (48%)	20 (45%)	16 (42%)	10 (31%)
Renal, fibrosis		2 (5%)		
Renal, hemorrhage	10 (32%)	17 (39%)	19 (50%)	12 (38%)
Renal, hyperplasia, lymphoid			1 (3%)	2 (6%)
Renal, hyperplasia, plasma cell		1 (2%)	6 (16%)	2 (6%)
Renal, pigmentation			3 (8%)	
Lymph node, mandibular	(48)	(49)	(47)	(48)
Congestion		5 (10%)	1 (2%)	4 (8%)
Ectasia	15 (31%)	8 (16%)	10 (21%)	10 (21%)
Hemorrhage	3 (6%)	1 (2%)	3 (6%)	1 (2%)
Hyperplasia, lymphoid		1 (2%)		1 (2%)
Hyperplasia, plasma cell	4 (8%)	8 (16%)	6 (13%)	4 (8%)
Lymph node, mesenteric	(46)	(50)	(50)	(50)
Atrophy		6 (12%)	1 (2%)	2 (4%)
Ectasia	5 (11%)	6 (12%)	6 (12%)	5 (10%)
Hemorrhage	12 (26%)	14 (28%)	12 (24%)	12 (24%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	2 (4%)	5 (10%)
Hyperplasia, plasma cell		2 (4%)		1 (2%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Hematopoietic System (continued)				
Spleen	(49)	(50)	(49)	(49)
Angiectasis	1 (2%)			
Atrophy	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Congestion	1 (2%)		1 (2%)	
Fibrosis		1 (2%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)		2 (4%)
Hyperplasia, lymphoid	1 (2%)			
Necrosis	1 (2%)			
Artery, mineralization	1 (2%)	1 (2%)		
Thymus	(48)	(49)	(49)	(50)
Atrophy	15 (31%)	29 (59%)	28 (57%)	24 (48%)
Cyst	5 (10%)	6 (12%)	4 (8%)	6 (12%)
Ectopic parathyroid gland	3 (6%)	5 (10%)	1 (2%)	1 (2%)
Ectopic thyroid	1 (2%)			
Fibrosis			1 (2%)	
Hemorrhage	8 (17%)	6 (12%)	8 (16%)	14 (28%)
Hyperplasia, lymphoid	1 (2%)			
Hyperplasia, squamous				2 (4%)
Artery, mineralization		1 (2%)		
Epithelial cell, hyperplasia			1 (2%)	
Integumentary System				
Mammary gland	(48)	(46)	(44)	(46)
Cyst		2 (4%)		1 (2%)
Hyperplasia	4 (8%)		2 (5%)	4 (9%)
Artery, mineralization	3 (6%)	5 (11%)		
Duct, dilatation	6 (13%)	7 (15%)	5 (11%)	4 (9%)
Skin	(50)	(50)	(50)	(50)
Cyst	1 (2%)	2 (4%)	1 (2%)	
Hyperkeratosis	1 (2%)			
Hyperplasia, squamous		2 (4%)	1 (2%)	2 (4%)
Inflammation, chronic	1 (2%)	2 (4%)		1 (2%)
Inflammation, suppurative		1 (2%)		1 (2%)
Ulcer	1 (2%)	1 (2%)		2 (4%)
Hair follicle, cyst	1 (2%)			1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	10 (20%)	21 (42%)	16 (32%)	6 (12%)
Inflammation, chronic active		1 (2%)		
Osteosclerosis			1 (2%)	
Cartilage, degeneration				1 (2%)
Cranium, fibrous osteodystrophy	10 (20%)	15 (30%)	13 (26%)	2 (4%)
Joint, arthrosis				1 (2%)
Joint, fibrosis				1 (2%)
Joint, inflammation, chronic			1 (2%)	1 (2%)
Mandible, hyperplasia				1 (2%)
Metacarpal, inflammation, chronic active				1 (2%)
Metatarsal, hyperplasia			1 (2%)	
Metatarsal, inflammation, chronic active				1 (2%)
Periosteum, hyperplasia				1 (2%)
Rib, callus		1 (2%)		
Vertebra, fibrous osteodystrophy		4 (8%)	2 (4%)	
Vertebra, inflammation, chronic				1 (2%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Nervous System				
Brain	(50)	(49)	(50)	(50)
Degeneration		1 (2%)		
Hemorrhage	1 (2%)	1 (2%)		
Hydrocephalus	1 (2%)	1 (2%)		
Peripheral nerve	(1)	(4)	(2)	(5)
Degeneration	1 (100%)			
Mineralization		2 (50%)	2 (100%)	
Radicular neuropathy		4 (100%)	1 (50%)	2 (40%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion		4 (8%)	2 (4%)	4 (8%)
Edema		2 (4%)		
Hemorrhage	2 (4%)	1 (2%)	10 (20%)	7 (14%)
Inflammation, acute	1 (2%)	3 (6%)		
Inflammation, chronic	1 (2%)		1 (2%)	
Inflammation, granulomatous	4 (8%)	1 (2%)	5 (10%)	2 (4%)
Mineralization		1 (2%)		
Necrosis	1 (2%)		1 (2%)	
Alveolar epithelium, hyperplasia	1 (2%)		2 (4%)	
Alveolar epithelium, hypertrophy		1 (2%)		
Alveolus, infiltration cellular, histiocyte	8 (16%)	5 (10%)	4 (8%)	
Alveolus, mineralization	2 (4%)			
Artery, mineralization	2 (4%)	3 (6%)		
Bronchus, inflammation, acute	1 (2%)			
Bronchus, mineralization	1 (2%)			
Interstitial, fibrosis	4 (8%)	6 (12%)	4 (8%)	1 (2%)
Interstitial, inflammation, chronic		2 (4%)		
Nose	(50)	(50)	(50)	(50)
Cyst	1 (2%)			
Erosion	1 (2%)			
Foreign body	11 (22%)	4 (8%)	6 (12%)	1 (2%)
Hemorrhage	3 (6%)		1 (2%)	
Hyperplasia, squamous	1 (2%)			
Inflammation, acute	7 (14%)	7 (14%)	4 (8%)	2 (4%)
Inflammation, chronic	7 (14%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic active	4 (8%)	6 (12%)	5 (10%)	6 (12%)
Metaplasia, squamous		1 (2%)	1 (2%)	2 (4%)
Thrombosis			1 (2%)	
Ulcer			2 (4%)	
Artery, thrombosis				1 (2%)
Olfactory epithelium, hyperplasia	1 (2%)			
Olfactory epithelium, metaplasia			1 (2%)	
Respiratory epithelium, hyperplasia	20 (40%)	9 (18%)	12 (24%)	15 (30%)
Respiratory epithelium, metaplasia		1 (2%)		
Respiratory epithelium, metaplasia, squamous			1 (2%)	
Trachea	(50)	(50)	(50)	(50)
Cyst		1 (2%)		
Foreign body			1 (2%)	
Inflammation, acute		1 (2%)		
Inflammation, chronic active				1 (2%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Special Senses System				
Eye			(1)	
Cornea, ulcer			1 (100%)	
Harderian gland	(1)		(4)	(1)
Inflammation, chronic				1 (100%)
Lacrimal gland			(1)	
Atrophy			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Congestion	4 (8%)			2 (4%)
Cyst	21 (42%)	31 (62%)	19 (38%)	16 (32%)
Hydronephrosis	19 (38%)	20 (40%)	30 (60%)	15 (30%)
Inflammation, acute		2 (4%)		1 (2%)
Mineralization	8 (16%)	17 (34%)	8 (16%)	5 (10%)
Nephropathy	50 (100%)	50 (100%)	50 (100%)	50 (100%)
Artery, mineralization	5 (10%)	8 (16%)	3 (6%)	
Renal tubule, accumulation, hyaline droplet			1 (2%)	1 (2%)
Renal tubule, hyperplasia	6 (12%)	17 (34%)	8 (16%)	5 (10%)
Vein, thrombosis		2 (4%)	1 (2%)	3 (6%)
Urinary bladder	(47)	(49)	(47)	(44)
Dilatation			1 (2%)	
Edema		1 (2%)		
Hemorrhage			1 (2%)	
Inflammation, acute		1 (2%)		
Inflammation, chronic	1 (2%)			
Inflammation, chronic active			1 (2%)	
Ulcer		1 (2%)		
Artery, mineralization			1 (2%)	
Transitional epithelium, hyperplasia	1 (2%)	3 (6%)	1 (2%)	

APPENDIX D **SUMMARY OF LESIONS IN MALE MICE** **IN THE 2-YEAR DRINKING WATER STUDY** **OF PYRIDINE**

TABLE D1	Summary of the Incidence of Neoplasms in Male Mice	
	in the 2-Year Drinking Water Study of Pyridine	D-2
TABLE D2	Individual Animal Tumor Pathology of Male Mice	
	in the 2-Year Drinking Water Study of Pyridine	D-6
TABLE D3	Statistical Analysis of Primary Neoplasms in Male Mice	
	in the 2-Year Drinking Water Study of Pyridine	D-28
TABLE D4	Historical Incidence of Liver Neoplasms in Untreated Male B6C3F₁ Mice	D-31
TABLE D5	Summary of the Incidence of Nonneoplastic Lesions in Male Mice	
	in the 2-Year Drinking Water Study of Pyridine	D-32

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine^a

	0 ppm	250 ppm	500 ppm	1,000 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	2	1	1	3
Moribund	2	3	3	1
Natural deaths	11	18	11	11
Survivors				
Other			1	
Terminal sacrifice	35	28	34	35
Animals examined microscopically	50	50	49	50
Alimentary System				
Intestine small, duodenum	(43)	(44)	(43)	(44)
Intestine small, jejunum	(40)	(46)	(42)	(44)
Carcinoma				1 (2%)
Histiocytic sarcoma			1 (2%)	
Liver	(50)	(50)	(49)	(50)
Hemangioma		1 (2%)		
Hemangiosarcoma	1 (2%)			
Hemangiosarcoma, multiple		2 (4%)		
Hepatoblastoma	1 (2%)	14 (28%)	16 (33%)	13 (26%)
Hepatoblastoma, multiple	1 (2%)	4 (8%)	6 (12%)	2 (4%)
Hepatocellular carcinoma	12 (24%)	16 (32%)	15 (31%)	22 (44%)
Hepatocellular carcinoma, multiple	3 (6%)	19 (38%)	26 (53%)	18 (36%)
Hepatocellular adenoma	13 (26%)	11 (22%)	5 (10%)	11 (22%)
Hepatocellular adenoma, multiple	16 (32%)	29 (58%)	29 (59%)	28 (56%)
Hepatocholangiocarcinoma, multiple		1 (2%)		
Histiocytic sarcoma	1 (2%)	2 (4%)		
Mast cell tumor malignant, metastatic, skin			1 (2%)	
Sarcoma, metastatic, mesentery		1 (2%)		
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Mesentery	(2)	(7)	(6)	(4)
Hepatocholangiocarcinoma, metastatic, liver		1 (14%)		
Histiocytic sarcoma		1 (14%)		
Sarcoma		1 (14%)	1 (17%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (25%)
Pancreas	(49)	(50)	(48)	(50)
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Stomach, forestomach	(49)	(50)	(48)	(49)
Squamous cell papilloma	1 (2%)			
Stomach, glandular	(49)	(50)	(48)	(47)
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Cardiovascular System				
Heart	(50)	(50)	(49)	(50)

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Endocrine System				
Adrenal cortex	(49)	(49)	(49)	(49)
Adenoma	1 (2%)			1 (2%)
Sarcoma, metastatic, mesentery		1 (2%)		
Capsule, adenoma	2 (4%)			
Capsule, sarcoma, metastatic, mesentery			1 (2%)	
Capsule, squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Adrenal medulla	(48)	(48)	(49)	(49)
Pheochromocytoma benign		1 (2%)		
Sarcoma, metastatic, mesentery		1 (2%)		
Islets, pancreatic	(49)	(50)	(48)	(50)
Adenoma		1 (2%)	2 (4%)	1 (2%)
Thyroid gland	(49)	(50)	(49)	(50)
Follicular cell, adenoma	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Follicular cell, adenoma, multiple			1 (2%)	
General Body System				
Peritoneum				(1)
Squamous cell carcinoma, metastatic, uncertain primary site				1 (100%)
Tissue NOS			(1)	
Thoracic, hemangiosarcoma			1 (100%)	
Genital System				
Coagulating gland		(1)		
Sarcoma, metastatic, mesentery		1 (100%)		
Epididymis	(50)	(50)	(49)	(50)
Sarcoma		1 (2%)		
Sarcoma, metastatic, mesentery		1 (2%)	1 (2%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Preputial gland	(50)	(50)	(49)	(49)
Sarcoma, metastatic, mesentery			1 (2%)	
Prostate	(50)	(48)	(48)	(49)
Sarcoma, metastatic, mesentery			1 (2%)	
Seminal vesicle	(49)	(49)	(49)	(50)
Sarcoma, metastatic, mesentery		1 (2%)	1 (2%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Testes	(50)	(50)	(49)	(50)
Sarcoma, metastatic, mesentery		1 (2%)	1 (2%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Hematopoietic System				
Bone marrow	(49)	(50)	(49)	(50)
Hemangiosarcoma		1 (2%)		
Hemangiosarcoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma	1 (2%)	1 (2%)		
Mast cell tumor malignant, metastatic, skin			1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Hematopoietic System (continued)				
Lymph node	(2)	(4)	(4)	(2)
Mediastinal, hepatocholangiocarcinoma, metastatic, liver		1 (25%)		
Mediastinal, sarcoma, metastatic, mesentery		1 (25%)	1 (25%)	
Mediastinal, squamous cell carcinoma, metastatic, uncertain primary site				1 (50%)
Lymph node, mandibular	(48)	(47)	(48)	(50)
Mast cell tumor malignant, metastatic, skin			1 (2%)	
Squamous cell carcinoma, metastatic, skin	1 (2%)			
Lymph node, mesenteric	(43)	(47)	(44)	(50)
Hemangioma		1 (2%)	1 (2%)	
Histiocytic sarcoma		1 (2%)	1 (2%)	
Sarcoma, metastatic, mesentery			1 (2%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Spleen	(49)	(50)	(47)	(49)
Hemangiosarcoma	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Hemangiosarcoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Mast cell tumor malignant, metastatic, skin			1 (2%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Thymus	(46)	(46)	(39)	(47)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Sarcoma, metastatic, mesentery			1 (3%)	
Integumentary System				
Skin	(49)	(50)	(48)	(50)
Squamous cell carcinoma	1 (2%)			
Subcutaneous tissue, basal cell adenoma				1 (2%)
Subcutaneous tissue, hemangioma		1 (2%)		1 (2%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, histiocytic sarcoma		1 (2%)		
Subcutaneous tissue, mast cell tumor malignant			1 (2%)	
Musculoskeletal System				
Skeletal muscle		(3)	(2)	(1)
Hepatoblastoma, metastatic, liver		1 (33%)		
Sarcoma, metastatic, mesentery		1 (33%)	1 (50%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (100%)
Nervous System				
Brain	(50)	(50)	(49)	(50)
Histiocytic sarcoma		1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Respiratory System				
Lung	(49)	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	10 (20%)	5 (10%)	7 (14%)	6 (12%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)		1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hemangiosarcoma, metastatic, liver		1 (2%)		
Hepatoblastoma, metastatic, liver		4 (8%)	7 (14%)	3 (6%)
Hepatocellular carcinoma, metastatic, liver	7 (14%)	7 (14%)	11 (22%)	13 (26%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Mediastinum, hepatocellular carcinoma, metastatic, liver		1 (2%)		
Mediastinum, hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Nose	(50)	(49)	(49)	(50)
Special Senses System				
Harderian gland	(5)			(1)
Adenoma	3 (60%)			1 (100%)
Carcinoma	2 (40%)			
Urinary System				
Kidney	(49)	(50)	(48)	(50)
Hemangiosarcoma, metastatic, tissue NOS			1 (2%)	
Histiocytic sarcoma		1 (2%)		
Mast cell tumor malignant, metastatic, skin			1 (2%)	
Sarcoma, metastatic, mesentery			1 (2%)	
Renal tubule, adenoma		1 (2%)	1 (2%)	
Urinary bladder	(48)	(49)	(44)	(50)
Hemangioma			1 (2%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Transitional epithelium, papilloma	1 (2%)			
Systemic Lesions				
Multiple organs ^b	(50)	(50)	(49)	(50)
Histiocytic sarcoma	1 (2%)	2 (4%)	1 (2%)	
Lymphoma malignant	3 (6%)	3 (6%)	3 (6%)	1 (2%)
Mesothelioma malignant			1 (2%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms ^c	43	49	48	47
Total primary neoplasms	79	122	122	114
Total animals with benign neoplasms	35	42	36	39
Total benign neoplasms	51	53	49	54
Total animals with malignant neoplasms	22	46	47	42
Total malignant neoplasms	28	69	73	60
Total animals with metastatic neoplasms	8	12	19	14
Total metastatic neoplasms	8	30	35	30
Total animals with malignant neoplasms of uncertain primary site				1
				1

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	1	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7
	1	2	4	7	9	2	3	3	3	5	6	7	7	0	1	2	2	2	2	2	2	2	2	2	2
	8	0	2	4	8	1	3	7	9	3	3	0	2	6	4	2	2	2	2	2	2	2	2	2	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	3	4	2	3	0	1	4	0	3	2	2	2	2	3	1	1	1	1	1	1	1	2	2	2
	2	7	0	5	2	5	7	3	1	0	7	1	3	4	4	1	3	4	5	6	8	9	0	2	6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	+	+	A	A	+	A	A	+	A	+	+	+	+	+	M	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	A	+	+	+	+	+	+	A	M	A	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	+	A	A	A	A	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	A	+	A	+	A	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatoblastoma																									
Hepatoblastoma, multiple																									
Hepatocellular carcinoma					X	X		X						X		X									
Hepatocellular carcinoma, multiple									X												X	X			
Hepatocellular adenoma		X					X							X		X	X				X				
Hepatocellular adenoma, multiple														X			X			X	X				X
Histiocytic sarcoma										X															
Mesentery																									
Oral mucosa												+													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Tongue																									
Tooth	+	+	+	+	+	+			+	+	+	+	+	+				+	+	+		+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Adenoma																									
Capsule, adenoma						X																			
Adrenal medulla	+	+	+	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	M	+	+	+	M	+	+	+	+	+	A	M	+	M	M	M	+	+	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	I	A	+	+	+	+	+	+	+	M	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																		X					X		
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7			
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3			
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
	2	2	4	4	4	4	4	4	4	4	5	0	0	0	0	0	0	0	1	3	3	3	3	3			
	8	9	1	2	4	5	6	7	8	9	0	2	3	4	6	7	8	9	0	1	3	5	6	8	9		
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hemangiosarcoma																										1	
Hepatoblastoma												X														1	
Hepatoblastoma, multiple																								X		1	
Hepatocellular carcinoma				X		X	X	X	X	X												X				12	
Hepatocellular carcinoma, multiple																										3	
Hepatocellular adenoma	X												X	X	X	X		X				X				13	
Hepatocellular adenoma, multiple			X		X	X			X		X	X					X	X	X				X	X		16	
Histiocytic sarcoma																										1	
Mesentery				+			+																			2	
Oral mucosa																										1	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Squamous cell papilloma																							X			1	
Stomach, glandular	+	+</																									

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	1	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
	1	2	4	7	9	2	3	3	3	5	6	7	7	0	1	2	2	2	2	2	2	2	2	2
	8	0	2	4	8	1	3	7	9	3	3	0	2	6	4	2	2	2	2	2	2	2	2	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	3	4	2	3	0	1	4	0	3	2	2	2	2	3	1	1	1	1	1	1	2	2	2
	2	7	0	5	2	5	7	3	1	0	7	1	3	4	4	1	3	4	5	6	8	9	0	2
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X														
Lymph node			+						+															
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, skin			X																					
Lymph node, mesenteric	+	+	+	+	+	+	M	+	M	+	+	A	+	M	A	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Thymus	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	A	+	+	+	+	+	+	M	+
Integumentary System																								
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Squamous cell carcinoma																								
Subcutaneous tissue, hemangiosarcoma																X								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X											X		X					X	X		
Alveolar/bronchiolar adenoma, multiple																								
Alveolar/bronchiolar carcinoma														X										
Hepatocellular carcinoma, metastatic, liver							X	X													X	X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																								
Harderian gland						M			+							+								
Adenoma									X								X							
Carcinoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma							X																	
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X												
Lymphoma malignant																								

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

	0	2	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	
Number of Days on Study	0	3	2	3	4	4	6	8	9	9	0	3	4	5	7	7	8	9	9	0	1	2	2	2	
	8	7	2	2	6	9	1	7	1	5	8	8	5	0	4	6	7	0	2	6	2	5	2	2	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Carcass ID Number	7	7	6	6	9	8	7	7	9	8	5	5	8	7	8	5	6	6	6	7	6	8	5	5	
	8	0	3	9	4	9	5	7	7	1	2	9	8	4	0	7	8	7	1	9	2	5	1	3	
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Gallbladder	+	+	+	+	M	A	+	A	+	A	+	A	A	+	+	A	A	+	A	A	M	M	+	+	
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	
Intestine large, rectum	+	+	+	+	+	A	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	+	+	+	+	A	A	+	+	+	+	+	+	A	+	+	+	M	+	A	A	+	+	+	+	
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	A	+	A	+	A	+	A	A	+	+	+	+	
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	A	A	A	+	+	+	+	
Intestine small, ileum	+	+	+	A	A	A	+	+	+	A	+	+	A	+	+	+	+	A	A	A	+	A	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangioma																									
Hemangiosarcoma, multiple					X										X										
Hepatoblastoma							X			X		X						X	X				X	X	
Hepatoblastoma, multiple															X					X					
Hepatocellular carcinoma				X											X		X	X	X				X	X	
Hepatocellular carcinoma, multiple						X							X	X		X				X	X	X		X	
Hepatocellular adenoma					X		X						X					X					X		
Hepatocellular adenoma, multiple				X					X		X						X	X	X		X	X	X		
Hepatocholangiocarcinoma, multiple																		X							
Histiocytic sarcoma				X									X												
Sarcoma, metastatic, mesentery								X																	
Mesentery	+	+					+											+							
Hepatocholangiocarcinoma, metastatic, liver																		X							
Histiocytic sarcoma				X																					
Sarcoma								X																	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Tooth				+										+		+								+	
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Sarcoma, metastatic, mesentery								X																	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	
Pheochromocytoma benign																									
Sarcoma, metastatic, mesentery								X																	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																									
Parathyroid gland	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	M	M	+	+	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Follicular cell, adenoma																									
																			X						
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

Number of Days on Study	0	2	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7
	0	3	2	3	4	4	6	8	9	9	0	3	4	5	7	7	7	8	9	9	0	1	2	2	2
	8	7	2	2	6	9	1	7	1	5	8	8	5	0	4	6	7	0	2	6	2	5	2	2	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	7	6	6	9	8	7	7	9	8	5	5	8	7	8	5	6	6	6	7	6	8	5	5	5
	8	0	3	9	4	9	5	7	7	1	2	9	8	4	0	7	8	7	1	9	2	5	1	3	4
Genital System																									
Coagulating gland																									
Sarcoma, metastatic, mesentery								+																	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Sarcoma, metastatic, mesentery																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, liver																									
Histiocytic sarcoma																									
Lymph node																									
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																									
Mediastinal, sarcoma, metastatic, mesentery																									
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, liver																									
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	I	+	+	+	+	+	I	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																									
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	+	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, histiocytic sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Hepatoblastoma, metastatic, liver																									
Sarcoma, metastatic, mesentery																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Peripheral nerve																									
Spinal cord																									

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7		
Number of Days on Study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3		
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0		
	5	5	5	6	6	6	6	7	7	7	7	8	8	8	8	9	9	9	9	9	0	8	9	9		
	5	6	8	0	4	5	6	1	2	3	6	2	3	4	6	0	1	2	3	8	9	0	7	5	6	
Genital System																										
Coagulating gland																										Total
Sarcoma, metastatic, mesentery																										Tissues/
																										Tumors
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Sarcoma																										1
Sarcoma, metastatic, mesentery																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Prostate	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Seminal vesicle	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Sarcoma, metastatic, mesentery																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Sarcoma, metastatic, mesentery																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma																										50
Hemangiosarcoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Lymph node																										1
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																										4
Mediastinal, sarcoma, metastatic, mesentery																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	
Hemangioma																										47
Histiocytic sarcoma																										47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma																										1
Hemangiosarcoma, metastatic, liver																										50
Histiocytic sarcoma																										3
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	
Hepatocellular carcinoma, metastatic, liver																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Subcutaneous tissue, hemangioma																										1
Subcutaneous tissue, histiocytic sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle																										50
Hepatoblastoma, metastatic, liver																										3
Sarcoma, metastatic, mesentery																										1
																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma																										50
Peripheral nerve																										1
Spinal cord																										1

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

	0	2	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	
Number of Days on Study	0	3	2	3	4	4	6	8	9	9	0	3	4	5	7	7	7	8	9	9	0	1	2	2	2	
	8	7	2	2	6	9	1	7	1	5	8	8	5	0	4	6	7	0	2	6	2	5	2	2	2	
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	7	7	6	6	9	8	7	7	9	8	5	5	8	7	8	5	6	6	6	7	6	8	5	5	5	
	8	0	3	9	4	9	5	7	7	1	2	9	8	4	0	7	8	7	1	9	2	5	1	3	4	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma						X																X				
Alveolar/bronchiolar carcinoma																										
Hemangiosarcoma, metastatic, liver														X												
Hepatoblastoma, metastatic, liver										X								X						X		
Hepatocellular carcinoma, metastatic, liver														X	X				X		X		X			
Hepatocholangiocarcinoma, metastatic, liver																		X								
Histiocytic sarcoma			X																							
Mediastinum, hepatocellular carcinoma, metastatic, liver																					X					
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																		X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma												X														
Renal tubule, adenoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma			X									X														
Lymphoma malignant									X						X				X							

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

Number of Days on Study	0	2	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	0	2	1	1	2	8	2	3	3	4	4	5	6	6	0	2	2	2	2	2	2	2	2
	3	6	3	4	6	6	3	0	7	2	3	7	1	4	8	2	2	2	2	2	2	2	2
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	2	2	0	1	2	2	0	2	3	3	4	1	3	0	0	0	0	0	0	1	1	1	1
	4	0	1	6	6	7	3	5	6	1	8	5	7	5	4	2	6	7	8	0	1	2	3
Alimentary System																							
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	A	M	A	+	+	M	A	A	A	M	+	+	+	+	+	M	+	+	+
Intestine large, colon	+	+	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	A	+	+	+	M	A	+	A	A	A	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	A	A	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	A	+	+	+	+	+	A	A	+	A	A	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							
Intestine small, ileum	+	+	+	+	A	A	+	+	+	+	A	+	A	A	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma					X							X			X		X		X		X		X
Hepatoblastoma, multiple						X									X			X		X			
Hepatocellular carcinoma			X		X	X					X							X		X	X		
Hepatocellular carcinoma, multiple							X	X			X	X			X		X			X		X	X
Hepatocellular adenoma					X						X									X			
Hepatocellular adenoma, multiple			X			X						X	X		X		X	X	X		X	X	X
Mast cell tumor malignant, metastatic, skin																							
Mesentery						+			+											+		+	
Sarcoma										X													
Pancreas	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																							
Cardiovascular System																							
Blood vessel	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																							
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, sarcoma, metastatic, mesentery											X												
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X								X												
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M
Pituitary gland	+	+	+	+	+	+	M	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																							
Follicular cell, adenoma, multiple																							
General Body System																							
Tissue NOS											+												
Thoracic, hemangiosarcoma											X												

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

Number of Days on Study	0	2	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
	0	2	1	1	2	8	2	3	3	4	4	5	6	6	0	2	2	2	2	2	2	2	2	2	2
	3	6	3	4	6	6	3	0	7	2	3	7	1	4	8	2	2	2	2	2	2	2	2	2	2
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	2	2	0	1	2	2	0	2	3	3	4	1	3	0	0	0	0	0	0	1	1	1	1	1	1
	4	0	1	6	6	7	3	5	6	1	8	5	7	5	4	2	6	7	8	0	1	2	3	4	4
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery									X																
Penis		+																							
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery									X																
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Sarcoma, metastatic, mesentery									X																
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery									X																
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery									X																
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, skin																									
Lymph node									+			+							+						
Mediastinal, sarcoma, metastatic, mesentery									X																
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, skin																									
Lymph node, mesenteric	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								X	
Histiocytic sarcoma																									
Sarcoma, metastatic, mesentery									X																
Spleen	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Mast cell tumor malignant, metastatic, skin																									
Thymus	+	+	+	+	+	+	M	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery									X																
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, mast cell tumor malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+	+															
Sarcoma, metastatic, mesentery									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve									+																
Spinal cord									+																

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

	0	2	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7
Number of Days on Study	0	2	1	1	2	8	2	3	3	4	4	5	6	6	0	2	2	2	2	2	2	2	2
	3	6	3	4	6	6	3	0	7	2	3	7	1	4	8	2	2	2	2	2	2	2	2
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	2	2	0	1	2	2	0	2	3	3	4	1	3	0	0	0	0	0	0	1	1	1	1
	4	0	1	6	6	7	3	5	6	1	8	5	7	5	4	2	6	7	8	0	1	2	3
Respiratory System																							
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X					X									X				
Alveolar/bronchiolar adenoma, multiple																							
Alveolar/bronchiolar carcinoma																							
Hepatoblastoma, metastatic, liver					X														X	X		X	
Hepatocellular carcinoma, metastatic, liver							X			X												X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																							
None																							
Urinary System																							
Kidney	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, tissue NOS								X															
Mast cell tumor malignant, metastatic, skin																							
Sarcoma, metastatic, mesentery									X														
Renal tubule, adenoma																					X		
Urinary bladder	+	+	A	+	A	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																						X	
Systemic Lesions																							
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							
Lymphoma malignant																				X			
Mesothelioma malignant																							

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

	0	0	0	4	4	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7		
Number of Days on Study	0	0	5	0	3	9	2	3	4	6	7	8	8	9	0	2	2	2	2	2	2	2	2	2	2		
	3	9	9	6	2	4	4	9	9	5	2	0	6	9	9	2	2	2	2	2	2	2	2	2	2		
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
Carcass ID Number	5	7	6	7	7	7	9	6	7	5	8	9	5	5	8	5	5	5	5	5	6	6	6	6	6		
	6	0	8	3	5	1	4	6	4	7	8	8	4	3	4	1	2	5	8	9	0	1	3	4	5		
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Gallbladder	+	A	+	A	M	+	+	A	A	A	M	A	M	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, cecum	+	+	+	+	A	A	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, duodenum	+	A	+	A	A	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, jejunum	+	A	+	A	A	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+		
Carcinoma																					X						
Intestine small, ileum	+	A	+	A	A	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hepatoblastoma							X								X					X		X					
Hepatoblastoma, multiple																		X					X				
Hepatocellular carcinoma				X	X	X		X	X	X	X					X				X	X	X	X				
Hepatocellular carcinoma, multiple							X					X	X	X					X	X				X	X		
Hepatocellular adenoma					X							X	X					X			X				X		
Hepatocellular adenoma, multiple				X				X	X	X						X	X		X	X		X	X	X	X		
Squamous cell carcinoma, metastatic, uncertain primary site													X														
Mesentery								+					+		+												
Squamous cell carcinoma, metastatic, uncertain primary site															X												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Squamous cell carcinoma, metastatic, uncertain primary site															X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Stomach, glandular	+	+	+	+	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+		
Squamous cell carcinoma, metastatic, uncertain primary site													X														
Tooth																									+		
Cardiovascular System																											
Blood vessel	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenoma																				X							
Capsule, squamous cell carcinoma, metastatic, uncertain primary site												X															
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenoma																											
Parathyroid gland	+	+	+	+	+	M	+	M	+	M	+	M	+	+	M	+	M	+	+	+	+	+	M	M	+		
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Follicular cell, adenoma																				X							
General Body System																											
Peritoneum															+												
Squamous cell carcinoma, metastatic, uncertain primary site														X													

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

[illegible]

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

Number of Days on Study	0	0	0	4	4	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	0	5	0	3	9	2	3	4	6	7	8	8	9	0	2	2	2	2	2	2	2	2	2	2	2	2	2
	3	9	9	6	2	4	4	9	9	5	2	0	6	9	9	2	2	2	2	2	2	2	2	2	2	2	2	2
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	5	7	6	7	7	7	9	6	7	5	8	9	5	5	8	5	5	5	5	5	5	6	6	6	6	6	6	6
	6	0	8	3	5	1	4	6	4	7	8	8	4	3	4	1	2	5	8	9	0	1	3	4	5			
Special Senses System																												
Eye																												+
Harderian gland																												+
Adenoma																												X
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, uncertain primary site																												X
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																												X
Mesothelioma malignant																												X

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7		
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3		
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	Total Tissues/ Tumors		
	7	7	7	7	7	8	8	8	8	8	8	8	8	9	9	9	9	9	0	6	6	6	9	9			
	2	6	7	8	9	0	1	2	3	5	6	7	9	0	1	2	5	7	9	0	2	7	9	3		6	
Special Senses System																											
Eye																											1
Harderian gland																											1
Adenoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Squamous cell carcinoma, metastatic, uncertain primary site																											1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Lymphoma malignant																											1
Mesothelioma malignant																											1

TABLE D3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Adrenal Cortex: Adenoma				
Overall rate ^a	3/49 (6%)	0/49 (0%)	0/49 (0%)	1/49 (2%)
Adjusted rate ^b	6.8%	0.0%	0.0%	2.4%
Terminal rate ^c	2/35 (6%)	0/27 (0%)	0/34 (0%)	1/34 (3%)
First incidence (days)	598	e		722 (T)
Poly-3 test ^d	P=0.234N	P=0.134N	P=0.126N	P=0.321N
Harderian Gland: Adenoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/49 (0%)	1/50 (2%)
Adjusted rate	6.7%	0.0%	0.0%	2.3%
Terminal rate	1/35 (3%)	0/28 (0%)	0/34 (0%)	1/35 (3%)
First incidence (days)	633			722 (T)
Poly-3 test	P=0.235N	P=0.133N	P=0.130N	P=0.320N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	0/50 (0%)	0/49 (0%)	1/50 (2%)
Adjusted rate	11.1%	0.0%	0.0%	2.3%
Terminal rate	3/35 (9%)	0/28 (0%)	0/34 (0%)	1/35 (3%)
First incidence (days)	633			722 (T)
Poly-3 test	P=0.052N	P=0.038N	P=0.036N	P=0.111N
Liver: Hepatocellular Adenoma				
Overall rate	29/50 (58%)	40/50 (80%)	34/49 (69%)	39/50 (78%)
Adjusted rate	63.2%	88.0%	75.7%	84.9%
Terminal rate	24/35 (69%)	27/28 (96%)	27/34 (79%)	31/35 (89%)
First incidence (days)	520	522	513	406
Poly-3 test	P=0.031	P=0.003	P=0.134	P=0.011
Liver: Hepatocellular Carcinoma				
Overall rate	15/50 (30%)	35/50 (70%)	41/49 (84%)	40/50 (80%)
Adjusted rate	32.3%	78.7%	89.9%	85.1%
Terminal rate	9/35 (26%)	23/28 (82%)	32/34 (94%)	28/35 (80%)
First incidence (days)	574	522	513	406
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	37/50 (74%)	45/50 (90%)	45/49 (92%)	47/50 (94%)
Adjusted rate	78.0%	96.5%	96.8%	100.0%
Terminal rate	28/35 (80%)	28/28 (100%)	34/34 (100%)	35/35 (100%)
First incidence (days)	520	522	513	406
Poly-3 test	P<0.001	P=0.004	P=0.004	P<0.001
Liver: Hepatoblastoma				
Overall rate	2/50 (4%)	18/50 (36%)	22/49 (45%)	15/50 (30%)
Adjusted rate	4.5%	41.2%	49.8%	34.4%
Terminal rate	2/35 (6%)	11/28 (39%)	17/34 (50%)	13/35 (37%)
First incidence (days)	722 (T)	549	514	624
Poly-3 test	P=0.005	P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	17/50 (34%)	42/50 (84%)	45/49 (92%)	42/50 (84%)
Adjusted rate	36.7%	91.3%	96.8%	89.4%
Terminal rate	11/35 (31%)	26/28 (93%)	34/34 (100%)	30/35 (86%)
First incidence (days)	574	522	513	406
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001

TABLE D3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	38/50 (76%)	47/50 (94%)	46/49 (94%)	47/50 (94%)
Adjusted rate	80.1%	98.9%	98.5%	100.0%
Terminal rate	29/35 (83%)	28/28 (100%)	34/34 (100%)	35/35 (100%)
First incidence (days)	520	522	513	406
Poly-3 test	P<0.001	P=0.002	P=0.003	P<0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	12/49 (24%)	5/50 (10%)	8/49 (16%)	8/50 (16%)
Adjusted rate	27.0%	11.9%	18.5%	18.3%
Terminal rate	9/35 (26%)	4/28 (14%)	6/34 (18%)	6/35 (17%)
First incidence (days)	520	546	526	639
Poly-3 test	P=0.303N	P=0.065N	P=0.245N	P=0.239N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	13/49 (27%)	7/50 (14%)	9/49 (18%)	8/50 (16%)
Adjusted rate	29.1%	16.6%	20.8%	18.3%
Terminal rate	9/35 (26%)	6/28 (21%)	7/34 (21%)	6/35 (17%)
First incidence (days)	520	546	526	639
Poly-3 test	P=0.197N	P=0.130N	P=0.258N	P=0.174N
Spleen: Hemangiosarcoma				
Overall rate	1/49 (2%)	3/50 (6%)	1/47 (2%)	1/49 (2%)
Adjusted rate	2.3%	7.1%	2.4%	2.4%
Terminal rate	1/35 (3%)	2/28 (7%)	1/34 (3%)	1/35 (3%)
First incidence (days)	722 (T)	532	722 (T)	722 (T)
Poly-3 test	P=0.459N	P=0.292	P=0.748	P=0.755
All Organs: Hemangioma				
Overall rate	0/50 (0%)	3/50 (6%)	2/49 (4%)	1/50 (2%)
Adjusted rate	0.0%	7.2%	4.7%	2.3%
Terminal rate	0/35 (0%)	1/28 (4%)	2/34 (6%)	1/35 (3%)
First incidence (days)		680	722 (T)	722 (T)
Poly-3 test	P=0.536	P=0.107	P=0.225	P=0.493
All Organs: Hemangiosarcoma				
Overall rate	2/50 (4%)	4/50 (8%)	2/49 (4%)	1/50 (2%)
Adjusted rate	4.5%	9.4%	4.7%	2.3%
Terminal rate	1/35 (3%)	2/28 (7%)	1/34 (3%)	1/35 (3%)
First incidence (days)	706	532	630	722 (T)
Poly-3 test	P=0.276N	P=0.313	P=0.678	P=0.512N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	7/50 (14%)	4/49 (8%)	1/50 (2%)
Adjusted rate	4.5%	16.4%	9.4%	2.3%
Terminal rate	1/35 (3%)	3/28 (11%)	3/34 (9%)	1/35 (3%)
First incidence (days)	706	532	630	722 (T)
Poly-3 test	P=0.215N	P=0.067	P=0.316	P=0.512N
All Organs: Malignant Lymphoma				
Overall rate	3/50 (6%)	3/50 (6%)	3/49 (6%)	1/50 (2%)
Adjusted rate	6.6%	7.1%	6.9%	2.3%
Terminal rate	2/35 (6%)	0/28 (0%)	2/34 (6%)	1/35 (3%)
First incidence (days)	542	595	226	722 (T)
Poly-3 test	P=0.233N	P=0.632	P=0.643	P=0.322N

TABLE D3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
All Organs: Benign Neoplasms				
Overall rate	35/50 (70%)	42/50 (84%)	36/49 (73%)	39/50 (78%)
Adjusted rate	74.7%	91.2%	79.1%	84.9%
Terminal rate	27/35 (77%)	27/28 (96%)	28/34 (82%)	31/35 (89%)
First incidence (days)	520	522	513	406
Poly-3 test	P=0.275	P=0.023	P=0.398	P=0.157
All Organs: Malignant Neoplasms				
Overall rate	22/50 (44%)	46/50 (92%)	47/49 (96%)	42/50 (84%)
Adjusted rate	46.5%	94.8%	98.4%	89.4%
Terminal rate	13/35 (37%)	26/28 (93%)	34/34 (100%)	30/35 (86%)
First incidence (days)	542	237	226	406
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	43/50 (86%)	49/50 (98%)	48/49 (98%)	47/50 (94%)
Adjusted rate	88.7%	100.0%	100.0%	100.0%
Terminal rate	31/35 (89%)	28/28 (100%)	34/34 (100%)	35/35 (100%)
First incidence (days)	520	237	226	406
Poly-3 test	P=0.009	P=0.018	P=0.019	P=0.021

(T) Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, and spleen; for other tissues, denominator is number of animals necropsied.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by N.

^e Not applicable; no neoplasms in animal group

TABLE D4
Historical Incidence of Liver Neoplasms in Untreated Male B6C3F₁ Mice^a

	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma
Overall Historical Incidence				
Total	179/289 (61.9%)	80/289 (27.7%)	9/289 (3.1%)	212/289 (73.4%)
Standard deviation	9.1%	11.7%	5.0%	11.7%
Range	47%-70%	10%-42%	0%-12%	53%-81%

^a Data as of 1 August 1997

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Pyridine^a

	0 ppm	250 ppm	500 ppm	1,000 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	2	1	1	3
Moribund	2	3	3	1
Natural deaths	11	18	11	11
Survivors				
Other			1	
Terminal sacrifice	35	28	34	35
Animals examined microscopically	50	50	49	50
Alimentary System				
Gallbladder	(43)	(33)	(30)	(36)
Hyperplasia				1 (3%)
Infiltration cellular, lymphocyte	1 (2%)			
Ulcer				1 (3%)
Intestine large, colon	(48)	(48)	(46)	(50)
Inflammation, chronic active	1 (2%)			
Intestine large, cecum	(47)	(44)	(42)	(45)
Lymphoid tissue, hyperplasia			2 (5%)	1 (2%)
Lymphoid tissue, necrosis			1 (2%)	
Intestine small, jejunum	(40)	(46)	(42)	(44)
Peyer's patch, hyperplasia, lymphoid	1 (3%)	1 (2%)	3 (7%)	1 (2%)
Liver	(50)	(50)	(49)	(50)
Angiectasis	1 (2%)	1 (2%)		
Basophilic focus	3 (6%)	1 (2%)		
Clear cell focus	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Cyst			1 (2%)	
Eosinophilic focus	19 (38%)	22 (44%)	18 (37%)	15 (30%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)	
Hemorrhage	1 (2%)			
Infiltration cellular, mixed cell	1 (2%)	1 (2%)		1 (2%)
Mixed cell focus	4 (8%)	2 (4%)	1 (2%)	1 (2%)
Necrosis	3 (6%)	5 (10%)	7 (14%)	6 (12%)
Vacuolization cytoplasmic, diffuse	2 (4%)	1 (2%)		
Centrilobular, congestion	1 (2%)			
Centrilobular, hypertrophy				1 (2%)
Centrilobular, vacuolization cytoplasmic	1 (2%)	2 (4%)		6 (12%)
Periportal, vacuolization cytoplasmic	1 (2%)			2 (4%)
Mesentery	(2)	(7)	(6)	(4)
Fat, necrosis	2 (100%)	3 (43%)	1 (17%)	2 (50%)
Oral mucosa	(1)			
Ulcer	1 (100%)			
Pancreas	(49)	(50)	(48)	(50)
Acinus, atrophy	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Acinus, cytoplasmic alteration			1 (2%)	1 (2%)
Duct, cyst			1 (2%)	1 (2%)
Salivary glands	(48)	(50)	(49)	(50)
Infiltration cellular, lymphocyte	31 (65%)	33 (66%)	26 (53%)	34 (68%)
Stomach, forestomach	(49)	(50)	(48)	(49)
Inflammation, chronic				1 (2%)
Inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Ulcer				1 (2%)
Epithelium, hyperplasia		1 (2%)	2 (4%)	2 (4%)

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Alimentary System (continued)				
Stomach, glandular	(49)	(50)	(48)	(47)
Necrosis	2 (4%)	2 (4%)	4 (8%)	1 (2%)
Glands, dysplasia			2 (4%)	
Tooth	(42)	(10)	(1)	(3)
Developmental malformation	42 (100%)	10 (100%)	1 (100%)	3 (100%)
Cardiovascular System				
Blood vessel	(50)	(49)	(47)	(49)
Aorta, thrombosis	1 (2%)			
Heart	(50)	(50)	(49)	(50)
Cardiomyopathy			1 (2%)	
Mineralization		3 (6%)		
Thrombosis				1 (2%)
Artery, inflammation, chronic active	2 (4%)			
Myocardium, hypertrophy	1 (2%)			
Endocrine System				
Adrenal cortex	(49)	(49)	(49)	(49)
Cytoplasmic alteration	18 (37%)	13 (27%)	9 (18%)	11 (22%)
Hyperplasia	2 (4%)	1 (2%)	2 (4%)	
Vacuolization cytoplasmic	2 (4%)			1 (2%)
Capsule, hyperplasia	42 (86%)	29 (59%)	30 (61%)	29 (59%)
Islets, pancreatic	(49)	(50)	(48)	(50)
Hyperplasia		5 (10%)	2 (4%)	
Parathyroid gland	(31)	(35)	(40)	(31)
Cyst	1 (3%)	1 (3%)		
Pituitary gland	(46)	(47)	(45)	(49)
Cyst	1 (2%)	1 (2%)		
Pars distalis, hyperplasia			1 (2%)	
Thyroid gland	(49)	(50)	(49)	(50)
Infiltration cellular, lymphocyte		1 (2%)		
Follicle, cyst	1 (2%)			
Follicular cell, hyperplasia	8 (16%)	14 (28%)	20 (41%)	12 (24%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(49)	(50)
Angiectasis		1 (2%)		
Infiltration cellular, lymphocyte	1 (2%)	4 (8%)	4 (8%)	4 (8%)
Inflammation, granulomatous	1 (2%)	1 (2%)		3 (6%)
Penis			(1)	
Inflammation, chronic active			1 (100%)	
Preputial gland	(50)	(50)	(49)	(49)
Atrophy	48 (96%)	45 (90%)	47 (96%)	42 (86%)
Cyst	29 (58%)	25 (50%)	32 (65%)	28 (57%)
Inflammation, chronic	18 (36%)	18 (36%)	13 (27%)	12 (24%)
Inflammation, chronic active	4 (8%)	6 (12%)	3 (6%)	6 (12%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Genital System (continued)				
Prostate	(50)	(48)	(48)	(49)
Cyst	1 (2%)			
Hyperplasia	1 (2%)			1 (2%)
Inflammation, chronic	7 (14%)	3 (6%)	10 (21%)	8 (16%)
Inflammation, chronic active	1 (2%)			1 (2%)
Testes	(50)	(50)	(49)	(50)
Atrophy	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Mineralization	1 (2%)			
Interstitial cell, hyperplasia	1 (2%)			
Hematopoietic System				
Bone marrow	(49)	(50)	(49)	(50)
Atrophy	2 (4%)			
Erythroid cell, hyperplasia		1 (2%)		
Myeloid cell, hyperplasia	1 (2%)	1 (2%)		1 (2%)
Lymph node	(2)	(4)	(4)	(2)
Iliac, hyperplasia, lymphoid	1 (50%)			
Mediastinal, congestion	1 (50%)			
Pancreatic, hyperplasia, lymphoid		1 (25%)		
Renal, hemorrhage			2 (50%)	1 (50%)
Renal, necrosis			1 (25%)	
Lymph node, mandibular	(48)	(47)	(48)	(50)
Hyperplasia, lymphoid	3 (6%)		1 (2%)	1 (2%)
Hyperplasia, plasma cell	2 (4%)			
Necrosis			1 (2%)	
Lymph node, mesenteric	(43)	(47)	(44)	(50)
Angiectasis		2 (4%)		
Atrophy				1 (2%)
Hematopoietic cell proliferation	2 (5%)	3 (6%)	6 (14%)	1 (2%)
Hemorrhage	13 (30%)	10 (21%)	10 (23%)	12 (24%)
Hyperplasia, histiocytic	2 (5%)		1 (2%)	
Hyperplasia, lymphoid	1 (2%)	5 (11%)	3 (7%)	4 (8%)
Hyperplasia, plasma cell	1 (2%)	1 (2%)		
Necrosis			1 (2%)	
Spleen	(49)	(50)	(47)	(49)
Atrophy		2 (4%)	3 (6%)	
Hematopoietic cell proliferation	13 (27%)	30 (60%)	26 (55%)	23 (47%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	1 (2%)
Necrosis			1 (2%)	
Thymus	(46)	(46)	(39)	(47)
Atrophy	26 (57%)	21 (46%)	16 (41%)	16 (34%)
Cyst		1 (2%)		
Necrosis			1 (3%)	1 (2%)
Integumentary System				
Skin	(49)	(50)	(48)	(50)
Inflammation, chronic active	1 (2%)			
Ulcer	1 (2%)			
Subcutaneous tissue, edema	1 (2%)	1 (2%)		
Subcutaneous tissue, inflammation, acute		1 (2%)		
Subcutaneous tissue, inflammation, chronic active	1 (2%)	1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(49)	(50)
Hemorrhage		1 (2%)		
Inflammation, chronic active	1 (2%)			
Mineralization	41 (82%)	27 (54%)	30 (61%)	35 (70%)
Peripheral nerve		(1)	(1)	
Sciatic, degeneration		1 (100%)		
Respiratory System				
Lung	(49)	(50)	(49)	(50)
Congestion	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Hemorrhage		1 (2%)		
Infiltration cellular, lymphocyte		4 (8%)	2 (4%)	
Alveolar epithelium, hyperplasia	4 (8%)	8 (16%)	1 (2%)	2 (4%)
Alveolus, infiltration cellular, histiocyte	1 (2%)	2 (4%)	4 (8%)	1 (2%)
Nose	(50)	(49)	(49)	(50)
Foreign body	1 (2%)			
Olfactory epithelium, degeneration, hyaline	15 (30%)	31 (63%)	35 (71%)	7 (14%)
Olfactory epithelium, glands, hyperplasia	1 (2%)			
Respiratory epithelium, degeneration, hyaline	20 (40%)	10 (20%)	15 (31%)	2 (4%)
Respiratory epithelium, hyperplasia	20 (40%)	22 (45%)	11 (22%)	15 (30%)
Respiratory epithelium, inflammation, chronic active	2 (4%)	1 (2%)		1 (2%)
Special Senses System				
Eye	(1)			(1)
Cataract	1 (100%)			
Cornea, inflammation, chronic	1 (100%)			
Cornea, inflammation, chronic active				1 (100%)
Urinary System				
Kidney	(49)	(50)	(48)	(50)
Atrophy				1 (2%)
Cyst	4 (8%)	2 (4%)	4 (8%)	
Fibrosis		1 (2%)		
Hydronephrosis	1 (2%)			
Infarct	2 (4%)	1 (2%)	2 (4%)	6 (12%)
Infiltration cellular, lymphocyte	3 (6%)	1 (2%)	2 (4%)	6 (12%)
Inflammation, chronic active	2 (4%)			
Mineralization	2 (4%)	3 (6%)		
Nephropathy	34 (69%)	27 (54%)	25 (52%)	32 (64%)
Artery, inflammation, chronic	1 (2%)			
Artery, inflammation, chronic active	1 (2%)			
Renal tubule, accumulation, hyaline droplet		1 (2%)		
Renal tubule, dilatation		1 (2%)	2 (4%)	5 (10%)
Renal tubule, hyperplasia	3 (6%)		1 (2%)	1 (2%)
Renal tubule, pigmentation		5 (10%)	3 (6%)	2 (4%)
Urinary bladder	(48)	(49)	(44)	(50)
Infiltration cellular, lymphocyte	8 (17%)	7 (14%)	9 (20%)	8 (16%)

APPENDIX E

SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF PYRIDINE

TABLE E1	Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine	E-2
TABLE E2	Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine	E-6
TABLE E3	Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine	E-24
TABLE E4	Historical Incidence of Liver Neoplasms in Untreated Female B6C3F₁ Mice	E-27
TABLE E5	Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Pyridine	E-28

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine^a

	0 ppm	125 ppm	250 ppm	500 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	3	6	4	5
Moribund	3	2	3	5
Natural deaths	12	12	21	11
Survivors				
Terminal sacrifice	32	30	22	29
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Gallbladder	(37)	(40)	(33)	(34)
Intestine large, rectum	(44)	(48)	(47)	(47)
Intestine large, cecum	(44)	(49)	(40)	(45)
Leiomyosarcoma				1 (2%)
Intestine small, jejunum	(42)	(47)	(38)	(43)
Intestine small, ileum	(43)	(48)	(37)	(41)
Carcinoma				1 (2%)
Liver	(49)	(50)	(50)	(50)
Hemangioma				1 (2%)
Hepatoblastoma	1 (2%)	2 (4%)	6 (12%)	12 (24%)
Hepatoblastoma, multiple			3 (6%)	4 (8%)
Hepatocellular carcinoma	10 (20%)	12 (24%)	19 (38%)	11 (22%)
Hepatocellular carcinoma, multiple	3 (6%)	11 (22%)	14 (28%)	30 (60%)
Hepatocellular adenoma	13 (27%)	5 (10%)	6 (12%)	4 (8%)
Hepatocellular adenoma, multiple	24 (49%)	34 (68%)	37 (74%)	30 (60%)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Sarcoma, metastatic, skin	1 (2%)			
Mesentery	(17)	(18)	(13)	(13)
Hepatoblastoma, metastatic, liver			1 (8%)	1 (8%)
Histiocytic sarcoma		2 (11%)		
Lipoma		1 (6%)		
Sarcoma		2 (11%)		
Pancreas	(49)	(49)	(47)	(48)
Histiocytic sarcoma		2 (4%)		
Sarcoma, metastatic, mesentery		1 (2%)		
Salivary glands	(50)	(50)	(49)	(50)
Schwannoma malignant, metastatic, skin		1 (2%)		
Stomach, forestomach	(49)	(49)	(49)	(49)
Squamous cell papilloma		1 (2%)		
Stomach, glandular	(48)	(49)	(48)	(49)
Cardiovascular System				
Blood vessel	(48)	(47)	(47)	(47)
Aorta, histiocytic sarcoma		1 (2%)		
Heart	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Sarcoma, metastatic, skin			1 (2%)	

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Endocrine System				
Adrenal cortex	(49)	(50)	(48)	(50)
Carcinoma, multiple	1 (2%)			
Histiocytic sarcoma	1 (2%)	1 (2%)		
Sarcoma, metastatic, mesentery		1 (2%)		
Capsule, adenoma	1 (2%)			
Islets, pancreatic	(49)	(50)	(47)	(49)
Adenoma	1 (2%)	2 (4%)		
Pituitary gland	(47)	(44)	(42)	(46)
Pars distalis, adenoma	8 (17%)	9 (20%)	6 (14%)	2 (4%)
Thyroid gland	(50)	(50)	(50)	(50)
Follicular cell, adenoma	3 (6%)	2 (4%)	3 (6%)	3 (6%)
General Body System				
Peritoneum			(2)	
Hepatoblastoma, metastatic, liver			1 (50%)	
Tissue NOS			(2)	
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (50%)	
Hepatoblastoma, metastatic, liver			1 (50%)	
Genital System				
Clitoral gland	(47)	(48)	(48)	(45)
Ovary	(47)	(49)	(46)	(49)
Cystadenoma	4 (9%)	3 (6%)	1 (2%)	
Granulosa cell tumor benign	1 (2%)		1 (2%)	
Hemangioma				1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Sarcoma, metastatic, mesentery		1 (2%)		
Oviduct		(1)		
Schwannoma malignant, metastatic, skin		1 (100%)		
Uterus	(48)	(50)	(47)	(50)
Adenoma	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Polyp stromal	2 (4%)	1 (2%)		
Hematopoietic System				
Bone marrow	(49)	(50)	(49)	(50)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Lymph node	(10)	(10)	(7)	(7)
Iliac, histiocytic sarcoma	1 (10%)	1 (10%)		
Iliac, rhabdomyosarcoma, metastatic, skeletal muscle		1 (10%)		
Mediastinal, sarcoma, metastatic, mesentery		1 (10%)		
Mediastinal, sarcoma, metastatic, skin	1 (10%)			
Pancreatic, hepatoblastoma, metastatic, liver			1 (14%)	
Pancreatic, sarcoma, metastatic, mesentery		1 (10%)		
Lymph node, mandibular	(48)	(50)	(49)	(47)
Histiocytic sarcoma	2 (4%)	1 (2%)		
Sarcoma, metastatic, skin			1 (2%)	
Schwannoma malignant, metastatic, skin		1 (2%)		

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Hematopoietic System (continued)				
Lymph node, mesenteric	(48)	(47)	(43)	(45)
Hemangioma				1 (2%)
Hepatoblastoma, metastatic, liver			1 (2%)	1 (2%)
Histiocytic sarcoma	1 (2%)	2 (4%)		
Spleen	(49)	(50)	(48)	(49)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Thymus	(45)	(44)	(46)	(39)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Histiocytic sarcoma		1 (2%)		
Integumentary System				
Skin	(49)	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)		
Subcutaneous tissue, hemangioma			1 (2%)	
Subcutaneous tissue, hemangiosarcoma			1 (2%)	
Subcutaneous tissue, sarcoma	2 (4%)	2 (4%)	3 (6%)	4 (8%)
Subcutaneous tissue, schwannoma malignant	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Musculoskeletal System				
Skeletal muscle		(1)	(1)	(1)
Hepatoblastoma, metastatic, liver			1 (100%)	
Rhabdomyosarcoma		1 (100%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	3 (6%)		3 (6%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Carcinoma, metastatic, harderian gland	1 (2%)			
Hepatoblastoma, metastatic, liver			1 (2%)	3 (6%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)		6 (12%)	10 (20%)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Rhabdomyosarcoma, metastatic, skeletal muscle		1 (2%)		
Sarcoma, metastatic, mesentery		1 (2%)		
Sarcoma, metastatic, skin			2 (4%)	
Schwannoma malignant, metastatic, skin		1 (2%)		
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Mediastinum, sarcoma, metastatic, skin			1 (2%)	
Mediastinum, schwannoma malignant, metastatic, skin		1 (2%)		
Nose	(50)	(50)	(47)	(50)
Sarcoma				1 (2%)
Sarcoma, metastatic, skin	1 (2%)			
Trachea	(50)	(50)	(50)	(50)

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Special Senses System				
Harderian gland	(1)	(1)		(1)
Adenoma		1 (100%)		
Carcinoma	1 (100%)			1 (100%)
Urinary System				
Kidney	(49)	(50)	(49)	(49)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Schwannoma malignant, metastatic, skin		1 (2%)		
Urinary bladder	(45)	(49)	(44)	(43)
Histiocytic sarcoma		1 (2%)		
Systemic Lesions				
Multiple organs ^b	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)	2 (4%)		
Leukemia granulocytic		1 (2%)		
Lymphoma malignant	6 (12%)	7 (14%)	4 (8%)	6 (12%)
Mesothelioma malignant				2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms ^c	47	45	45	45
Total primary neoplasms	90	105	108	122
Total animals with benign neoplasms	40	41	43	36
Total benign neoplasms	61	63	55	45
Total animals with malignant neoplasms	26	30	40	44
Total malignant neoplasms	29	42	53	77
Total animals with metastatic neoplasms	5	3	10	12
Total metastatic neoplasms	6	14	21	15

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

	0	1	3	4	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7
Number of Days on Study	6	5	7	7	5	6	6	2	4	4	6	7	8	9	9	1	1	1	2	2	2	2	2	2
	4	1	5	6	4	5	8	5	4	4	2	0	7	1	7	1	4	9	9	9	9	9	9	9
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	6	2	5	3	3	4	4	2	5	5	1	2	4	4	5	2	5	6	1	1	1	2	2	2
	4	7	8	5	0	8	4	6	0	3	7	8	5	7	6	4	7	3	6	8	9	0	1	2
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Histiocytic sarcoma			X																					
Lymph node				+			+	+	+							+	+					+		
Iliac, histiocytic sarcoma								X																
Mediastinal, sarcoma, metastatic, skin																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Histiocytic sarcoma			X					X																
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Histiocytic sarcoma								X																
Spleen	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Subcutaneous tissue, sarcoma																								
Subcutaneous tissue, schwannoma malignant																					X			
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+																					
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Alveolar/bronchiolar adenoma, multiple																								
Alveolar/bronchiolar carcinoma											X													
Carcinoma, metastatic, harderian gland																								
Hepatocellular carcinoma, metastatic, liver				X					X															
Histiocytic sarcoma			X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Harderian gland																								
Carcinoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Histiocytic sarcoma			X																					
Urinary bladder	+	+	+	+	+	A	+	+	+	A	A	+	A	+	+	+	A	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X					X																
Lymphoma malignant														X		X	X	X				X		

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

Number of Days on Study	0	0	0	1	3	4	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7		
	0	1	2	7	7	1	5	7	9	0	0	4	4	7	7	8	9	1	1	2	2	2	2	2	2		
	4	6	0	2	2	9	5	3	9	5	8	2	9	4	7	0	6	1	3	4	9	9	9	9	9		
Carcass ID Number	2	2	2	3	2	3	2	2	2	2	2	3	2	2	2	2	2	3	2	3	2	2	2	2	2		
	7	8	7	0	8	1	9	8	6	7	9	0	7	9	9	8	6	0	7	0	6	6	7	7	7		
	0	4	9	5	1	1	5	9	9	7	1	1	1	4	7	2	8	6	5	7	6	7	2	3	4		
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Gallbladder	A	+	+	A	+	+	A	+	A	+	A	+	A	+	+	A	+	A	A	+	+	+	+	+	+		
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+		
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+		
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	A	+	+	+	+	+	+	+	+		
Intestine small, ileum	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hepatoblastoma										X													X				
Hepatocellular carcinoma										X				X									X		X		
Hepatocellular carcinoma, multiple									X									X	X		X						
Hepatocellular adenoma										X				X		X		X									
Hepatocellular adenoma, multiple						X	X	X		X			X	X		X	X			X	X	X	X	X	X		
Histiocytic sarcoma																											
Mesentery							+	+	+		+				+	+		+		+					+		
Histiocytic sarcoma																											
Lipoma																X											
Sarcoma										X						X											
Pancreas	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Histiocytic sarcoma																											
Sarcoma, metastatic, mesentery																	X										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Schwannoma malignant, metastatic, skin													X														
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Squamous cell papilloma																											
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Cardiovascular System																											
Blood vessel	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+		
Aorta, histiocytic sarcoma																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Histiocytic sarcoma																											
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Histiocytic sarcoma																											
Sarcoma, metastatic, mesentery																	X										
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenoma																			X								
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	M	M	+	M	+	M	M	+	M	+	+	M	M	M	M		
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+		
Pars distalis, adenoma											X			X		X					X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Follicular cell, adenoma															X												
General Body System																											
None																											

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

Number of Days on Study	0	0	0	1	3	4	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7
	0	1	2	7	7	1	5	7	9	0	0	4	4	7	7	8	9	1	1	2	2	2	2	2	2
	4	6	0	2	2	9	5	3	9	5	8	2	9	4	7	0	6	1	3	4	9	9	9	9	9
Carcass ID Number	2	2	2	3	2	3	2	2	2	2	3	2	2	2	2	2	3	2	3	2	2	2	2	2	2
	7	8	7	0	8	1	9	8	6	7	9	0	7	9	9	8	6	0	7	0	6	6	7	7	7
	0	4	9	5	1	1	5	9	9	7	1	1	1	4	7	2	8	6	5	7	6	7	2	3	4
Genital System																									
Clitoral gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																		X						X	
Histiocytic sarcoma																									
Sarcoma, metastatic, mesentery																X									
Oviduct												+													
Schwannoma malignant, metastatic, skin												X													
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node									+		+			+	+	+			+						+
Iliac, histiocytic sarcoma																									
Iliac, rhabdomyosarcoma, metastatic, skeletal muscle																X									
Mediastinal, sarcoma, metastatic, mesentery																	X								
Pancreatic, sarcoma, metastatic, mesentery																	X								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Schwannoma malignant, metastatic, skin													X												
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+
Histiocytic sarcoma																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, sarcoma								X																X	
Subcutaneous tissue, schwannoma malignant													X												
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Rhabdomyosarcoma																X									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

Number of Days on Study	0	0	0	1	3	4	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7
	0	1	2	7	7	1	5	7	9	0	0	4	4	7	7	8	9	1	1	2	2	2	2	2	2
	4	6	0	2	2	9	5	3	9	5	8	2	9	4	7	0	6	1	3	4	9	9	9	9	9
Carcass ID Number	2	2	2	3	2	3	2	2	2	2	3	2	2	2	2	2	3	2	3	2	2	2	2	2	2
	7	8	7	0	8	1	9	8	6	7	9	0	7	9	9	8	6	0	7	0	6	6	7	7	7
	0	4	9	5	1	1	5	9	9	7	1	1	1	4	7	2	8	6	5	7	6	7	2	3	4
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X			X															
Alveolar/bronchiolar carcinoma																									
Histiocytic sarcoma																									
Rhabdomyosarcoma, metastatic, skeletal muscle																X									
Sarcoma, metastatic, mesentery																X									
Schwannoma malignant, metastatic, skin													X												
Mediastinum, schwannoma malignant, metastatic, skin													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Schwannoma malignant, metastatic, skin																X									
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia granulocytic												X													
Lymphoma malignant									X										X	X				X	

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

Number of Days on Study	0	0	0	1	4	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7
	0	3	4	7	1	0	5	6	8	2	3	3	4	4	5	7	8	9	9	9	9	0	0	0	1
	3	3	0	5	7	9	6	4	3	4	2	3	2	8	9	8	4	2	6	7	9	0	0	8	2
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	3	1	1	6	5	4	6	5	5	4	2	3	5	4	6	2	4	2	2	3	2	4	4	5
	9	7	6	8	0	4	2	5	2	5	8	0	4	7	7	4	7	5	2	4	6	6	3	1	9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	A	+	A	A	A	A	A	M	+	+	+	A	+	+	A	+	A	A	A	+	A	A	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	+	+	+	+	A	+	+	+	A	+	A	+	A	+	+	+	A	A	+	A	A	+
Intestine small, duodenum	A	A	A	+	+	M	+	A	+	+	+	A	+	+	A	+	A	+	+	A	+	+	A	+	+
Intestine small, jejunum	A	A	A	+	A	+	+	A	+	+	+	+	A	A	+	A	A	+	+	A	A	+	M	+	+
Intestine small, ileum	A	A	A	+	A	+	+	A	+	+	A	+	A	A	+	A	+	+	+	A	A	+	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma									X		X	X				X							X		
Hepatoblastoma, multiple								X																	
Hepatocellular carcinoma							X	X		X					X	X			X	X		X	X		
Hepatocellular carcinoma, multiple																							X		X
Hepatocellular adenoma							X							X		X									
Hepatocellular adenoma, multiple							X				X	X	X		X		X	X	X	X	X	X	X	X	X
Mesentery									+	+	+	+							+						
Hepatoblastoma, metastatic, liver														X											
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+
Salivary glands	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	M	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin														X											
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	M	M	A	+	+	+	+	+	+	+	A	M	+
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+
Parathyroid gland	+	M	+	M	+	+	M	+	A	+	M	+	M	+	M	+	+	M	+	M	M	+	+	M	M
Pituitary gland	+	I	M	+	+	+	+	+	+	+	I	M	I	+	+	+	+	+	+	+	+	+	M	M	+
Pars distalis, adenoma																						X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Peritoneum					+									+											
Hepatoblastoma, metastatic, liver														X											
Tissue NOS														+											
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Hepatoblastoma, metastatic, liver														X											
Genital System																									
Clitoral gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	M	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+
Cystadenoma																									
Granulosa cell tumor benign																						X			
Uterus	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

	0	0	0	1	4	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7		
Number of Days on Study	0	3	4	7	1	0	5	6	8	2	3	3	4	4	5	7	8	9	9	9	9	0	0	1	
	3	3	0	5	7	9	6	4	3	4	2	3	2	8	9	8	4	2	6	7	9	0	0	8	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		
Carcass ID Number	2	3	1	1	6	5	4	6	5	5	4	2	3	5	4	6	2	4	2	2	3	2	4	4	
	9	7	6	8	0	4	2	5	2	5	8	0	4	7	7	4	7	5	2	4	6	6	3	1	
Hematopoietic System																									
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lymph node										+	+		+	+				+		+	+	+	+		
Pancreatic, hepatoblastoma, metastatic, liver														X											
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Sarcoma, metastatic, skin															X										
Lymph node, mesenteric	M	A	+	+	+	+	+	+	+	+	A	+	+	A	+	M	+	+	+	A	+	+	+	+	
Hepatoblastoma, metastatic, liver														X											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, sarcoma								X						X									X		
Subcutaneous tissue, schwannoma malignant														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle														+											
Hepatoblastoma, metastatic, liver														X											
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar carcinoma																									
Hepatoblastoma, metastatic, liver														X											
Hepatocellular carcinoma, metastatic, liver																X							X		
Sarcoma, metastatic, skin															X							X			
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																									
Mediastinum, sarcoma, metastatic, skin																X									
Nose	+	A	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
Urinary bladder	+	A	+	+	M	+	+	A	+	+	+	+	+	A	+	+	+	+	A	A	+	+	+	+	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant										X					X		X	X							

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

	0	0	0	1	2	3	4	4	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7
Number of Days on Study	1	1	1	8	9	6	3	7	1	2	7	9	1	2	7	8	8	9	9	0	0	2	2	2	2
	2	4	5	8	9	6	0	9	0	6	1	5	5	6	7	0	6	0	0	0	3	9	9	9	9
Carcass ID Number	4	4	3	4	3	3	4	3	3	3	4	3	3	3	4	4	3	3	3	3	4	3	3	3	3
	1	0	9	0	9	7	1	9	9	7	1	8	8	9	0	0	7	8	9	7	0	6	6	6	6
	3	5	5	6	1	1	4	9	4	7	5	8	4	8	2	4	2	6	3	4	9	6	7	8	9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	+	+	A	+	+	+	+	+	A	A	A	A	M	M	A	M	A	+	M
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	A	A	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	A	+	A	+	+	+	+	+
Leiomyosarcoma																									
Intestine small, duodenum	A	+	+	+	+	+	+	+	A	+	+	+	+	+	A	A	A	A	+	A	A	+	+	+	+
Intestine small, jejunum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	M	+	A	A	A	+	+	+	+
Intestine small, ileum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	A	A	A	A	A	A	A	+	+	+	+
Carcinoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma															X										
Hepatoblastoma									X		X			X		X						X	X	X	
Hepatoblastoma, multiple																									
Hepatocellular carcinoma									X		X			X							X	X	X		
Hepatocellular carcinoma, multiple													X	X		X	X	X	X	X		X		X	X
Hepatocellular adenoma										X					X							X		X	
Hepatocellular adenoma, multiple						X			X	X	X	X	X	X					X	X	X				
Mesentery									+					+		+	+				+				
Hepatoblastoma, metastatic, liver																X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Cardiovascular System																									
Blood vessel	M	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	M	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																							X	X	
General Body System																									
None																									
Genital System																									
Clitoral gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Hemangioma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

[illegible]

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

	0	0	0	1	2	3	4	4	5	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7
Number of Days on Study	1	1	1	8	9	6	3	7	1	2	7	9	1	2	7	8	8	9	9	0	0	2	2	2
	2	4	5	8	9	6	0	9	0	6	1	5	5	6	7	0	6	0	0	0	3	9	9	9
Carcass ID Number	4	4	3	4	3	3	4	3	3	3	4	3	3	3	4	4	3	3	3	3	4	3	3	3
	1	0	9	0	9	7	1	9	9	7	1	8	8	9	0	0	7	8	9	7	0	6	6	6
	3	5	5	6	1	1	4	9	4	7	5	8	4	8	2	4	2	6	3	4	9	6	7	8
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+					+										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+
Lymph node, mesenteric	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	A	+	+
Hemangioma																								
Hepatoblastoma, metastatic, liver																	X							
Spleen	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	M	M	A	M	M	+	I
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma						X			X											X				
Subcutaneous tissue, schwannoma malignant																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle														+										
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X			
Alveolar/bronchiolar carcinoma												X			X						X			
Hepatoblastoma, metastatic, liver																						X		
Hepatocellular carcinoma, metastatic, liver																X		X		X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma								X																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Harderian gland																								
Carcinoma																								
Urinary System																								
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	A	A	A	A	A	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant									X															
Mesothelioma malignant													X		X									

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7			
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9			
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4	Total Tissues/ Tumors		
	7	7	7	7	7	7	8	8	8	8	8	8	8	9	9	9	9	0	0	0	0	0	1	1		1	
	0	3	5	6	8	9	0	1	2	3	5	7	9	0	2	6	7	0	1	3	7	8	0	1		2	
Hematopoietic System																											
Bone marrow	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Lymph node				+												+	+				+	+			7		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45		
Hemangioma												X													1		
Hepatoblastoma, metastatic, liver																									1		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	39		
Integumentary System																											
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Subcutaneous tissue, sarcoma							X																		4		
Subcutaneous tissue, schwannoma malignant																							X		1		
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Skeletal muscle																									1		
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Alveolar/bronchiolar adenoma	X				X																				3		
Alveolar/bronchiolar carcinoma																									3		
Hepatoblastoma, metastatic, liver																	X					X			3		
Hepatocellular carcinoma, metastatic, liver	X	X											X					X	X			X		X	10		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Sarcoma																									1		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Special Senses System																											
Harderian gland					+																				1		
Carcinoma					X																				1		
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43		
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Lymphoma malignant			X													X		X				X	X		6		
Mesothelioma malignant																									2		

TABLE E3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Liver: Hepatocellular Adenoma				
Overall rate ^a	37/49 (76%)	39/50 (78%)	43/50 (86%)	34/50 (68%)
Adjusted rate ^b	82.5%	87.9%	97.3%	79.1%
Terminal rate ^c	27/32 (84%)	27/30 (90%)	22/22 (100%)	23/29 (79%)
First incidence (days)	554	419	509	430
Poly-3 test ^d	P=0.372N	P=0.336	P=0.015	P=0.442N
Liver: Hepatocellular Carcinoma				
Overall rate	13/49 (27%)	23/50 (46%)	33/50 (66%)	41/50 (82%)
Adjusted rate	29.8%	55.0%	78.1%	97.1%
Terminal rate	8/32 (25%)	18/30 (60%)	20/22 (91%)	29/29 (100%)
First incidence (days)	476	573	556	479
Poly-3 test	P<0.001	P=0.014	P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	41/49 (84%)	42/50 (84%)	44/50 (88%)	44/50 (88%)
Adjusted rate	89.9%	94.6%	98.4%	99.5%
Terminal rate	29/32 (91%)	29/30 (97%)	22/22 (100%)	29/29 (100%)
First incidence (days)	476	419	509	430
Poly-3 test	P=0.011	P=0.323	P=0.081	P=0.045
Liver: Hepatoblastoma				
Overall rate	1/49 (2%)	2/50 (4%)	9/50 (18%)	16/50 (32%)
Adjusted rate	2.4%	4.9%	21.6%	39.6%
Terminal rate	1/32 (3%)	1/30 (3%)	3/22 (14%)	12/29 (41%)
First incidence (days)	729 (T)	599	564	510
Poly-3 test	P<0.001	P=0.493	P=0.007	P<0.001
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	13/49 (27%)	23/50 (46%)	36/50 (72%)	43/50 (86%)
Adjusted rate	29.8%	55.0%	82.8%	99.0%
Terminal rate	8/32 (25%)	18/30 (60%)	20/22 (91%)	29/29 (100%)
First incidence (days)	476	573	556	479
Poly-3 test	P<0.001	P=0.014	P<0.001	P<0.001
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	41/49 (84%)	42/50 (84%)	45/50 (90%)	44/50 (88%)
Adjusted rate	89.9%	94.6%	99.6%	99.5%
Terminal rate	29/32 (91%)	29/30 (97%)	22/22 (100%)	29/29 (100%)
First incidence (days)	476	419	509	430
Poly-3 test	P=0.009	P=0.323	P=0.042	P=0.045
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/50 (4%)	3/50 (6%)	0/50 (0%)	3/50 (6%)
Adjusted rate	4.7%	7.2%	0.0%	7.8%
Terminal rate	2/32 (6%)	1/30 (3%)	0/22 (0%) ^e	2/29 (7%)
First incidence (days)	729 (T)	555		703
Poly-3 test	P=0.463	P=0.486	P=0.254N	P=0.455
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted rate	4.7%	2.5%	5.0%	7.6%
Terminal rate	1/32 (3%)	1/30 (3%)	1/22 (5%)	0/29 (0%)
First incidence (days)	662	729 (T)	727	595
Poly-3 test	P=0.287	P=0.521N	P=0.665	P=0.460

TABLE E3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	4/50 (8%)	4/50 (8%)	2/50 (4%)	5/50 (10%)
Adjusted rate	9.3%	9.6%	5.0%	12.7%
Terminal rate	3/32 (9%)	2/30 (7%)	1/22 (5%)	2/29 (7%)
First incidence (days)	662	555	727	595
Poly-3 test	P=0.399	P=0.624	P=0.374N	P=0.445
Ovary: Cystadenoma				
Overall rate	4/47 (9%)	3/49 (6%)	1/46 (2%)	0/49 (0%)
Adjusted rate	9.9%	7.6%	2.7%	0.0%
Terminal rate	4/32 (13%)	2/29 (7%)	1/21 (5%)	0/29 (0%)
First incidence (days)	729 (T)	696	729 (T)	
Poly-3 test	P=0.029N	P=0.513N	P=0.210N	P=0.069N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	8/47 (17%)	9/44 (20%)	6/42 (14%)	2/46 (4%)
Adjusted rate	19.7%	25.0%	17.1%	5.7%
Terminal rate	8/31 (26%)	6/26 (23%)	5/21 (24%)	2/27 (7%)
First incidence (days)	729 (T)	608	700	729 (T)
Poly-3 test	P=0.041N	P=0.391	P=0.502N	P=0.071N
Skin (Subcutaneous Tissue): Sarcoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted rate	4.7%	4.9%	7.4%	9.9%
Terminal rate	2/32 (6%)	1/30 (3%)	0/22 (0%)	1/29 (3%)
First incidence (days)	729 (T)	573	556	299
Poly-3 test	P=0.197	P=0.679	P=0.477	P=0.311
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted rate	7.0%	4.9%	7.6%	7.8%
Terminal rate	3/32 (9%)	1/30 (3%)	3/22 (14%)	3/29 (10%)
First incidence (days)	729 (T)	674	729 (T)	729 (T)
Poly-3 test	P=0.472	P=0.522N	P=0.628	P=0.615
All Organs: Hemangioma				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	2.5%	7.7%
Terminal rate	0/32 (0%)	0/30 (0%)	1/22 (5%)	2/29 (7%)
First incidence (days)			729 (T)	615
Poly-3 test	P=0.017		P=0.485	P=0.103
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	5.0%	7.7%
Terminal rate	0/32 (0%)	0/30 (0%)	1/22 (5%)	2/29 (7%)
First incidence (days)			723	615
Poly-3 test	P=0.022		P=0.221	P=0.103
All Organs: Malignant Lymphoma				
Overall rate	6/50 (12%)	7/50 (14%)	4/50 (8%)	6/50 (12%)
Adjusted rate	13.9%	17.1%	9.8%	15.3%
Terminal rate	2/32 (6%)	5/30 (17%)	0/22 (0%)	5/29 (17%)
First incidence (days)	687	599	624	510
Poly-3 test	P=0.546N	P=0.460	P=0.407N	P=0.554

TABLE E3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
All Organs: Benign Neoplasms				
Overall rate	40/50 (80%)	41/50 (82%)	43/50 (86%)	36/50 (72%)
Adjusted rate	85.5%	91.5%	97.3%	83.7%
Terminal rate	28/32 (88%)	28/30 (93%)	22/22 (100%)	25/29 (86%)
First incidence (days)	151	419	509	430
Poly-3 test	P=0.445N	P=0.275	P=0.035	P=0.527N
All Organs: Malignant Neoplasms				
Overall rate	26/50 (52%)	30/50 (60%)	40/50 (80%)	44/50 (88%)
Adjusted rate	56.0%	69.7%	90.1%	99.2%
Terminal rate	14/32 (44%)	20/30 (67%)	20/22 (91%)	29/29 (100%)
First incidence (days)	375	573	556	299
Poly-3 test	P<0.001	P=0.128	P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	47/50 (94%)	45/50 (90%)	45/50 (90%)	45/50 (90%)
Adjusted rate	96.5%	99.7%	99.6%	99.7%
Terminal rate	31/32 (97%)	30/30 (100%)	22/22 (100%)	29/29 (100%)
First incidence (days)	151	419	509	299
Poly-3 test	P=0.174	P=0.348	P=0.366	P=0.347

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by N.

^e Not applicable; no neoplasms in animal group

TABLE E4
Historical Incidence of Liver Neoplasms in Untreated Female B6C3F₁ Mice^a

	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma
Overall Historical Incidence				
Total	150/289 (51.9%)	55/289 (19.0%)	0/289	173/289 (59.9%)
Standard deviation	20.8%	13.7%		21.3%
Range	26%-80%	8%-42%		32%-82%

^a Data as of 1 August 1997

TABLE E5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Pyridine^a

	0 ppm	125 ppm	250 ppm	500 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	3	6	4	5
Moribund	3	2	3	5
Natural deaths	12	12	21	11
Survivors				
Terminal sacrifice	32	30	22	29
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(37)	(40)	(33)	(34)
Hyperplasia				1 (3%)
Intestine large, rectum	(44)	(48)	(47)	(47)
Artery, necrosis				1 (2%)
Intestine large, cecum	(44)	(49)	(40)	(45)
Edema			1 (3%)	
Intestine small, jejunum	(42)	(47)	(38)	(43)
Peyer s patch, hyperplasia, lymphoid	1 (2%)			
Intestine small, ileum	(43)	(48)	(37)	(41)
Peyer s patch, hyperplasia, lymphoid		1 (2%)		
Liver	(49)	(50)	(50)	(50)
Basophilic focus	1 (2%)			
Clear cell focus	1 (2%)	5 (10%)	1 (2%)	2 (4%)
Cyst			1 (2%)	
Eosinophilic focus	17 (35%)	12 (24%)	14 (28%)	9 (18%)
Hematopoietic cell proliferation	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Hemorrhage	1 (2%)			
Infiltration cellular, lymphocyte	4 (8%)			
Mixed cell focus	5 (10%)	4 (8%)	3 (6%)	
Necrosis	5 (10%)	2 (4%)	5 (10%)	7 (14%)
Vacuolization cytoplasmic, diffuse	1 (2%)			1 (2%)
Centrilobular, congestion				1 (2%)
Centrilobular, degeneration			1 (2%)	1 (2%)
Midzonal, vacuolization cytoplasmic			1 (2%)	
Periportal, vacuolization cytoplasmic		2 (4%)	1 (2%)	
Mesentery	(17)	(18)	(13)	(13)
Infiltration cellular, lymphocyte	1 (6%)			
Inflammation, chronic active	2 (12%)			
Fat, necrosis	12 (71%)	13 (72%)	11 (85%)	9 (69%)
Pancreas	(49)	(49)	(47)	(48)
Infiltration cellular, lymphocyte	1 (2%)	1 (2%)		
Inflammation, chronic active	1 (2%)			2 (4%)
Acinus, atrophy		2 (4%)	1 (2%)	2 (4%)
Artery, inflammation, chronic			1 (2%)	
Duct, cyst		1 (2%)	2 (4%)	2 (4%)
Salivary glands	(50)	(50)	(49)	(50)
Infiltration cellular, lymphocyte	33 (66%)	35 (70%)	36 (73%)	29 (58%)
Stomach, forestomach	(49)	(49)	(49)	(49)
Ulcer	1 (2%)			
Epithelium, hyperplasia	1 (2%)			
Stomach, glandular	(48)	(49)	(48)	(49)
Necrosis	3 (6%)	3 (6%)	4 (8%)	3 (6%)
Tooth	(2)			
Developmental malformation	2 (100%)			

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE E5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Cardiovascular System				
Blood vessel	(48)	(47)	(47)	(47)
Aorta, inflammation, chronic active	1 (2%)			
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	1 (2%)			
Inflammation, chronic active	1 (2%)			
Mineralization			1 (2%)	
Atrium, thrombosis				1 (2%)
Endocrine System				
Adrenal cortex	(49)	(50)	(48)	(50)
Cytoplasmic alteration	2 (4%)			2 (4%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)	
Hemorrhage	1 (2%)			2 (4%)
Hyperplasia	1 (2%)			
Capsule, hyperplasia	41 (84%)	35 (70%)	39 (81%)	37 (74%)
Adrenal medulla	(49)	(49)	(45)	(49)
Hyperplasia	1 (2%)	2 (4%)		
Islets, pancreatic	(49)	(50)	(47)	(49)
Hyperplasia			2 (4%)	3 (6%)
Parathyroid gland	(31)	(29)	(30)	(36)
Infiltration cellular, lymphocyte				1 (3%)
Pituitary gland	(47)	(44)	(42)	(46)
Hemorrhage				1 (2%)
Pars distalis, angiectasis		1 (2%)		1 (2%)
Pars distalis, hyperplasia	5 (11%)	4 (9%)	6 (14%)	8 (17%)
Pars intermedia, hyperplasia	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
Infiltration cellular, lymphocyte		3 (6%)		3 (6%)
C-cell, hyperplasia	1 (2%)			
Follicle, cyst	4 (8%)		1 (2%)	
Follicular cell, hyperplasia	14 (28%)	21 (42%)	22 (44%)	23 (46%)
General Body System				
Peritoneum			(2)	
Inflammation, chronic active			1 (50%)	
Genital System				
Clitoral gland	(47)	(48)	(48)	(45)
Atrophy	45 (96%)	43 (90%)	45 (94%)	43 (96%)
Cyst	3 (6%)			
Inflammation, chronic	2 (4%)	2 (4%)	1 (2%)	4 (9%)
Inflammation, chronic active	2 (4%)		3 (6%)	
Pigmentation	2 (4%)		1 (2%)	3 (7%)
Ovary	(47)	(49)	(46)	(49)
Angiectasis		1 (2%)		
Cyst	14 (30%)	9 (18%)	11 (24%)	11 (22%)
Periovarian tissue, hyperplasia, lymphoid		1 (2%)		
Uterus	(48)	(50)	(47)	(50)
Congestion	1 (2%)			
Cyst	3 (6%)	3 (6%)	5 (11%)	2 (4%)
Hyperplasia, cystic	44 (92%)	43 (86%)	38 (81%)	39 (78%)
Inflammation, chronic active	1 (2%)			1 (2%)
Pigmentation				1 (2%)

TABLE E5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Hematopoietic System				
Bone marrow	(49)	(50)	(49)	(50)
Atrophy	1 (2%)	1 (2%)		
Myeloid cell, hyperplasia	1 (2%)			2 (4%)
Lymph node	(10)	(10)	(7)	(7)
Iliac, hemorrhage	1 (10%)			
Iliac, hyperplasia, lymphoid	3 (30%)		2 (29%)	
Iliac, inflammation, chronic active				1 (14%)
Iliac, pigmentation	1 (10%)			
Inguinal, hyperplasia, lymphoid			1 (14%)	
Mediastinal, hemorrhage	1 (10%)		1 (14%)	
Mediastinal, hyperplasia, plasma cell		1 (10%)		
Mediastinal, inflammation, chronic active	1 (10%)			
Mediastinal, pigmentation			1 (14%)	
Renal, hemorrhage			1 (14%)	
Renal, hyperplasia, lymphoid	1 (10%)			
Lymph node, mandibular	(48)	(50)	(49)	(47)
Hemorrhage	3 (6%)		1 (2%)	1 (2%)
Hyperplasia, lymphoid	2 (4%)	2 (4%)		
Lymph node, mesenteric	(48)	(47)	(43)	(45)
Angiectasis			1 (2%)	2 (4%)
Ectasia		1 (2%)		
Hematopoietic cell proliferation	1 (2%)			1 (2%)
Hemorrhage	4 (8%)	2 (4%)	3 (7%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		
Artery, necrosis				1 (2%)
Spleen	(49)	(50)	(48)	(49)
Atrophy		1 (2%)	1 (2%)	
Hematopoietic cell proliferation	29 (59%)	27 (54%)	32 (67%)	39 (80%)
Hemorrhage		1 (2%)	1 (2%)	
Hyperplasia, lymphoid	2 (4%)	5 (10%)	4 (8%)	2 (4%)
Inflammation, chronic active	1 (2%)			
Pigmentation	1 (2%)			1 (2%)
Thymus	(45)	(44)	(46)	(39)
Atrophy	11 (24%)	11 (25%)	13 (28%)	10 (26%)
Ectopic parathyroid gland	1 (2%)		2 (4%)	
Hyperplasia, lymphoid	1 (2%)		1 (2%)	
Inflammation, acute	1 (2%)			
Necrosis	2 (4%)	4 (9%)	3 (7%)	3 (8%)
Integumentary System				
Mammary gland	(47)	(50)	(49)	(48)
Hyperplasia	2 (4%)	1 (2%)		
Skin	(49)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, necrosis		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy		5 (10%)	2 (4%)	
Hyperostosis	1 (2%)			

TABLE E5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Nervous System				
Brain	(50)	(50)	(50)	(50)
Cyst epithelial inclusion				1 (2%)
Hemorrhage	1 (2%)	1 (2%)		
Infiltration cellular, histiocyte		1 (2%)		
Mineralization	25 (50%)	27 (54%)	18 (36%)	19 (38%)
Meninges, inflammation, chronic active	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion		2 (4%)	4 (8%)	3 (6%)
Hemorrhage	1 (2%)			1 (2%)
Infiltration cellular, lymphocyte	4 (8%)	2 (4%)		1 (2%)
Inflammation, chronic active	1 (2%)			
Alveolar epithelium, hyperplasia	5 (10%)	3 (6%)	1 (2%)	
Alveolus, infiltration cellular, histiocyte	2 (4%)			2 (4%)
Nose	(50)	(50)	(47)	(50)
Foreign body	1 (2%)			
Olfactory epithelium, degeneration, hyaline	19 (38%)	27 (54%)	35 (74%)	36 (72%)
Olfactory epithelium, inflammation, chronic active				1 (2%)
Olfactory epithelium, necrosis		1 (2%)		
Respiratory epithelium, degeneration, hyaline	26 (52%)	16 (32%)	12 (26%)	13 (26%)
Respiratory epithelium, hyperplasia	12 (24%)	8 (16%)	12 (26%)	4 (8%)
Respiratory epithelium, inflammation, chronic active	3 (6%)			1 (2%)
Respiratory epithelium, necrosis		1 (2%)		
Special Senses System				
None				
Urinary System				
Kidney	(49)	(50)	(49)	(49)
Infarct	1 (2%)	2 (4%)	1 (2%)	
Infiltration cellular, plasma cell				1 (2%)
Infiltration cellular, lymphocyte	4 (8%)	2 (4%)	5 (10%)	2 (4%)
Nephropathy	5 (10%)	10 (20%)	7 (14%)	8 (16%)
Glomerulus, amyloid deposition			1 (2%)	
Renal tubule, dilatation		1 (2%)	2 (4%)	2 (4%)
Renal tubule, pigmentation			3 (6%)	2 (4%)
Renal tubule, regeneration		1 (2%)		1 (2%)
Urinary bladder	(45)	(49)	(44)	(43)
Infiltration cellular, lymphocyte	16 (36%)	16 (33%)	17 (39%)	22 (51%)

APPENDIX F

GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL	F-2
MOUSE LYMPHOMA MUTAGENICITY TEST PROTOCOL	F-2
CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS	F-3
DROSOPHILA MELANOGASTER TEST PROTOCOLS	F-4
MOUSE BONE MARROW CYTOGENETIC TEST PROTOCOLS	F-5
RESULTS	F-6
TABLE F1 Mutagenicity of Pyridine in <i>Salmonella typhimurium</i>	F-7
TABLE F2 Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Pyridine	F-8
TABLE F3 Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Pyridine	F-10
TABLE F4 Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Pyridine	F-11
TABLE F5 Induction of Sex-Linked Recessive Lethal Mutations in <i>Drosophila melanogaster</i> by Pyridine	F-12
TABLE F6 Induction of Reciprocal Translocations in <i>Drosophila melanogaster</i> by Pyridine	F-13
TABLE F7 Induction of Chromosomal Aberrations in Mouse Bone Marrow Cells by Pyridine	F-13
TABLE F8 Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Mice Treated with Pyridine by Intraperitoneal Injection	F-14

GENETIC TOXICOLOGY

***SALMONELLA* MUTAGENICITY TEST PROTOCOL**

Testing was performed as reported by Haworth *et al.* (1983). Pyridine was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of pyridine; 10,000 µg/plate was selected as the high dose. All trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose-related, is not reproducible, or is not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

MOUSE LYMPHOMA MUTAGENICITY TEST PROTOCOL

The experimental protocol is presented in detail by McGregor *et al.* (1988). Pyridine was supplied as a coded aliquot by Radian Corporation. The high dose of pyridine did not exceed 5,000 µg/mL in the absence of toxicity. L5178Y mouse lymphoma cells were maintained at 37° C as suspension cultures in supplemented Fischer's medium; normal cycling time was approximately 10 hours. To reduce the number of spontaneously occurring cells resistant to trifluorothymidine (TFT), subcultures were exposed to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day; to medium containing thymidine, hypoxanthine, and glycine for 1 day; and to normal medium for 3 to 5 days. For cloning, the horse serum content was increased and Noble agar was added.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 mL medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with pyridine continued for 4 hours, at which time the medium plus pyridine was removed, and the cells were resuspended in fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, cells were plated in medium and soft agar supplemented with TFT for selection of TFT-resistant cells, and cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% CO₂ for 10 to 12 days. The test was initially performed without S9. Because a clearly positive response was not obtained, the test was repeated using freshly prepared S9 from the livers of Aroclor 1254-induced male 344 rats.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Caspary *et al.* (1988). All data were evaluated statistically for trend and peak responses. Both responses had to be significant ($P \leq 0.05$) for pyridine to be considered positive, i.e., capable of inducing TFT resistance. A single significant response led to a questionable conclusion, and the absence of both a trend and a peak response resulted in a negative call.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Pyridine was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for

induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of pyridine; the high dose was limited by toxicity or, in the absence of toxicity, 5,000 $\mu\text{g/mL}$ was selected as the high dose. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with pyridine in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing pyridine was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with pyridine, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no pyridine. Incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind, and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P < 0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with pyridine for 11.5 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with pyridine and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 11.5 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. Two-hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

***DROSOPHILA MELANOGASTER* TEST PROTOCOLS**

The assays for induction sex-linked recessive lethal (SLRL) mutations and chromosomal reciprocal translocations (RTs) were performed with adult flies as described by Valencia *et al.* (1985) and Mason *et al.* (1992). Pyridine was supplied as a coded aliquot by Radian Corporation.

Sex-Linked Recessive Lethal Mutation Test: Pyridine was assayed in the SLRL test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because no clearly positive response was obtained in the feeding experiments, it was retested by injection into adult males.

To administer pyridine by injection, a glass Pasteur pipette was drawn out in a flame to a microfine filament, and the tip was broken off to allow delivery of the test solution. Injection was performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution (0.2-0.3 μ L) to slightly distend the abdomen of the fly, or by attaching the pipette to a microinjector that automatically delivered a calibrated volume. Flies were anesthetized with ether and immobilized on a strip of tape. Injection into the thorax, under the wing, was performed with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of pyridine at a level that would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. Canton-S males were allowed to feed for 72 hours on a solution of pyridine in 5% sucrose. In the injection experiments, 24- to 72-hour old Canton-S males were treated with a solution of pyridine dissolved in saline and allowed to recover for 24 hours. A concurrent saline control group was also included. In the adult exposures, treated males were mated to three *Basc* females for 3 days and were given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days (in each case, sample sperm from successive matings were treated at successively earlier postmeiotic stages). F₁ heterozygous females were mated with their siblings and then placed in individual vials. F₁ daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as vials containing fewer than 5% of the expected number of wild-type males after 17 days; these were retested to confirm the response.

SLRL data were analyzed by simultaneous comparison with the concurrent and historical controls (Mason *et al.*, 1992) using a normal approximation to the binomial test (Margolin *et al.*, 1983). A test result was considered positive if the P value was less or equal to 0.01 and the mutation frequency in the tested group was greater than 0.10% or if the P value was less than or equal to 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if the P value was between 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15% or if the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 0.10%. A test was considered negative if the P value was greater than or equal to 0.10 or if the frequency in the treatment group was less than 0.10%.

Reciprocal Translocation Test: Because one of the injection experiments (Mason *et al.*, 1992) produced a positive result in the SLRL test, pyridine was assayed for induction of RTs using the same exposure method. The treatment regimen was essentially the same as that for the SLRL test, except that Canton-S males were mated *en masse* to marker (*bw;st* or *bw;e*) females. The females were transferred to fresh medium every 3 to 4 days for a period of about 3 weeks to produce a total of six broods. The results of the SLRL test were used to determine the germ cell stages most likely to be affected by pyridine. F₁ heterozygous males were backcrossed individually to *bw;st* females, and the F₂ progeny were screened for pseudolinkage, which results from the induction of a translocation in a germ cell of the parental male. Flies suspected of carrying RTs were retested to confirm the findings. The translocation data were analyzed according to the conditional binomial response test of Kastenbaum and Bowman (1970).

MOUSE BONE MARROW CYTOGENETIC TEST PROTOCOLS

Chromosomal Aberrations Test: A dose range-finding study was performed in the absence of adequate toxicity information from the literature, and the highest dose was limited by toxicity. Pyridine was tested for induction of Abs in mouse bone marrow by two different protocols. The first protocol used a standard harvest time of 17 hours, and the second protocol used a delayed harvest time of 36 hours.

Male B6C3F₁ mice (10 animals per dose group) were injected intraperitoneally with pyridine dissolved in phosphate-buffered saline (PBS) (injection volume=0.4 mL). Solvent control mice received equivalent injections of PBS alone. The positive control was mitomycin C. The mice were subcutaneously implanted with a BrdU tablet (McFee *et al.*, 1983) 18 hours before the scheduled harvest. (For the standard protocol, this required BrdU implantation to precede injection with pyridine by 1 hour). The use of BrdU allowed selection of the appropriate cell population for scoring. (Abs induced by chemical administration are present in maximum number at the first metaphase following treatment; they decline in number during subsequent nuclear divisions due to cell death.) Two hours before sacrifice, the mice received an intraperitoneal injection of colchicine in saline. The animals were killed 17 or 36 hours after pyridine injection (18 hours after BrdU dosing). One or both femurs were removed, and the marrow was flushed out with PBS (pH 7.0). Cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. After a 24-hour drying period, the slides were stained and scored.

Fifty first-division metaphase cells were scored from each of eight animals per group. Responses were evaluated as the percentage of aberrant metaphase cells, excluding gaps. The data were analyzed by a trend test (Margolin *et al.*, 1986).

Micronucleus Test: Preliminary range-finding studies were performed. Factors affecting dose selection included chemical solubility and toxicity and the extent of cell cycle delay induced by pyridine exposure. The standard three-exposure protocol is described in detail by Shelby *et al.* (1993). Male B6C3F₁ mice were injected intraperitoneally three times at 24-hour intervals with pyridine dissolved in PBS; the total dosing volume was 0.4 mL. Solvent control animals were injected with 0.4 mL of PBS only. The positive control animals received injections of cyclophosphamide. The animals were killed 24 hours after the third injection, and blood smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in each of five animals per dose group. In addition, the percentage of PCEs among the total erythrocyte population in the bone marrow was scored for each dose group as a measure of toxicity.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among PCEs was analyzed by a statistical software package that tested for increasing trend over dose groups using a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the control group (Margolin *et al.*, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dose group is less than or equal to 0.025 divided by the number of dose groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitude of those effects.

RESULTS

Pyridine (100-10,000 µg/plate) was not mutagenic in *S. typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9 metabolic activation enzymes (Haworth *et al.*, 1983; Table F1). Further, no significant increase in mutant frequencies was observed in L5178Y mouse lymphoma cells, tested with and without S9 metabolic activation (McGregor *et al.*, 1988; Table F2). In cytogenetic tests with cultured CHO cells, pyridine did not induce SCEs (Table F3) or Abs (Table F4), with or without S9. At the highest viable dose (1,673 µg/mL) tested for SCE induction in the absence of S9, pyridine induced marked cell

cycle delay, and an extended culture time (31 hours) was used to allow sufficient cells to accumulate for analysis.

Pyridine was tested on three separate occasions in two different laboratories for induction of SLRL mutations in adult male *D. melanogaster* (Valencia *et al.*, 1985; Mason *et al.*, 1992; Table F5), and mixed results were obtained. In the first experiment (Valencia *et al.*, 1985), administration of pyridine by injection (7,000 ppm in aqueous 0.7% saline solution) gave negative ($P=0.225$) results, but feeding (700 ppm pyridine in aqueous 5% sucrose) produced an increase in recessive lethal mutations that was considered to be equivocal ($P=0.043$). A second experiment performed in the same laboratory using both injection (500 ppm) and feeding (729 ppm) yielded negative results. In the third experiment (Mason *et al.*, 1992) performed in a second laboratory, results of a feeding (500 ppm) experiment were negative ($P=0.998$), but administration of pyridine by injection (4,300 ppm) induced a significant increase in the frequency of SLRL mutations ($P=0.008$). This positive result in the SLRL test led to the performance of a test for induction of RTs in germ cells of treated male *D. melanogaster* (Mason *et al.*, 1992; Table F6); results of this test were negative.

In vivo assays for chromosomal effects were conducted with male mice. No induction of Abs (Table F7) was noted in bone marrow cells at either of two sampling times (400-600 mg/kg pyridine; single injection), and no increase in the frequency of micronucleated PCEs (Table F8) was noted in bone marrow after intraperitoneal injection of pyridine (up to 500 mg/kg administered three times at 24-hour intervals).

In summary, with the exception of the single positive result obtained in a *D. melanogaster* SLRL assay, no indication of mutagenic activity was seen with pyridine in a variety of *in vitro* and *in vivo* assays for gene mutation and chromosomal damage.

TABLE F1
Mutagenicity of Pyridine in *Salmonella typhimurium*^a

Strain	Dose ($\mu\text{g}/\text{plate}$)	Revertants/plate ^b					
		S9		+10% hamster S9		+10% rat S9	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	115 \pm 8.3	105 \pm 3.5	116 \pm 9.8	107 \pm 14.4	113 \pm 2.4	105 \pm 8.0
	100	106 \pm 6.4	113 \pm 1.5	116 \pm 5.4	131 \pm 10.5	119 \pm 6.4	107 \pm 17.0
	333.3	93 \pm 3.6	114 \pm 5.5	103 \pm 1.7	131 \pm 8.6	129 \pm 3.1	112 \pm 15.1
	1,000	96 \pm 5.2	114 \pm 16.5	94 \pm 2.3	115 \pm 5.8	127 \pm 1.3	117 \pm 3.0
	3,333.3	93 \pm 0.0	105 \pm 4.6	121 \pm 6.9	135 \pm 12.2	122 \pm 8.3	114 \pm 3.9
	10,000	96 \pm 10.7	117 \pm 8.4	94 \pm 2.8	148 \pm 4.8	112 \pm 8.1	119 \pm 10.7
Trial summary		Negative	Negative	Negative	Equivocal	Negative	Negative
Positive control ^c		483 \pm 7.2	416 \pm 11.3	1,119 \pm 119.8	2,115 \pm 14.6	1,075 \pm 30.0	549 \pm 71.3
TA1535	0	31 \pm 0.7	21 \pm 5.6	12 \pm 2.3	12 \pm 1.9	11 \pm 1.8	14 \pm 0.9
	100	34 \pm 1.3	21 \pm 4.8	9 \pm 1.5	13 \pm 2.3	14 \pm 0.6	15 \pm 3.7
	333.3	29 \pm 5.6	18 \pm 1.2	11 \pm 2.1	11 \pm 2.3	12 \pm 1.3	12 \pm 0.6
	1,000	27 \pm 4.0	18 \pm 1.5	10 \pm 2.5	12 \pm 1.8	14 \pm 2.3	11 \pm 1.2
	3,333.3	32 \pm 3.8	17 \pm 2.0	14 \pm 1.9	11 \pm 1.8	11 \pm 1.7	12 \pm 0.9
	10,000	33 \pm 7.1	17 \pm 4.0	14 \pm 5.3	14 \pm 1.2	13 \pm 4.1	15 \pm 1.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		412 \pm 9.4	346 \pm 14.4	257 \pm 13.8	266 \pm 9.5	314 \pm 14.9	167 \pm 4.9
TA1537	0	9 \pm 1.3	5 \pm 1.5	18 \pm 3.5	10 \pm 0.7	23 \pm 2.1	6 \pm 1.0
	100	13 \pm 5.7	6 \pm 1.2	20 \pm 1.9	7 \pm 0.6	20 \pm 1.0	7 \pm 0.7
	333.3	9 \pm 0.6	6 \pm 0.9	18 \pm 4.9	8 \pm 2.3	17 \pm 2.2	4 \pm 1.5
	1,000	14 \pm 1.2	7 \pm 1.0	18 \pm 3.8	10 \pm 2.2	22 \pm 3.0	6 \pm 1.0
	3,333	10 \pm 3.0	5 \pm 0.3	20 \pm 4.7	9 \pm 1.7	17 \pm 2.7	5 \pm 0.6
	10,000	14 \pm 0.3	6 \pm 0.9	17 \pm 4.2	5 \pm 1.8	18 \pm 1.2	6 \pm 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		329 \pm 159.1	847 \pm 54.3	459 \pm 52.4	411 \pm 10.3	495 \pm 52.6	239 \pm 24.6
TA98	0	35 \pm 4.7	37 \pm 3.5	49 \pm 5.6	35 \pm 2.3	31 \pm 5.2	34 \pm 3.2
	100	35 \pm 4.9	33 \pm 3.5	45 \pm 2.0	39 \pm 0.3	41 \pm 2.4	40 \pm 0.3
	333.3	35 \pm 2.3	31 \pm 5.9	39 \pm 5.7	40 \pm 0.9	36 \pm 3.2	32 \pm 5.1
	1,000	33 \pm 4.9	29 \pm 2.3	46 \pm 7.5	37 \pm 2.6	34 \pm 1.5	38 \pm 0.3
	3,333	25 \pm 0.7	29 \pm 3.4	50 \pm 14.2	30 \pm 4.7	33 \pm 3.5	28 \pm 1.8
	10,000	22 \pm 3.5	27 \pm 3.8	43 \pm 6.4	43 \pm 7.8	30 \pm 5.6	26 \pm 5.6
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		691 \pm 10.1	671 \pm 57.5	570 \pm 57.5	1,271 \pm 7.8	574 \pm 22.3	365 \pm 22.9

^a Study was performed at SRI International. The detailed protocol and these data are presented in Haworth *et al.* (1983). 0 $\mu\text{g}/\text{plate}$ was the solvent control.

^b Revertants are presented as mean \pm standard error from three plates.

^c The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE F2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Pyridine^a

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction ^b	Average Mutant Fraction
S9						
Trial 1						
Medium ^c		112	102	95	28	
		99	106	86	29	
		108	103	100	31	
		101	89	92	31	30
Methyl methanesulfonate ^d	15	43	26	239	186	
		49	26	195	133	160*
Pyridine	625	89	100	99	37	
		105	102	95	30	34
	1,250	73	88	47	21	
		86	101	80	31	26
	2,500	94	69	81	29	
		78	71	56	24	26
	5,000	82	70	60	24	
		88	77	113	43	34
Trial 2						
Medium		76	98	89	39	
		99	102	136	46	
		84	97	122	49	
		65	102	120	62	49
Methyl methanesulfonate	15	27	23	440	550	
		24	20	473	671	610*
Pyridine	1,000	82	101	160	65	
		58	90	106	61	63
	2,000	74	77	154	69	
		68	78	167	81	75
	3,000	78	68	182	78	
		71	76	161	76	77*
	4,000	47	68	97	68	
		55	76	154	94	81*
5,000	48	57	138	97		
	69	66	151	73	85*	
Trial 3						
Medium		98	100	60	20	
		108	110	67	21	
		71	84	70	33	
		102	106	85	28	25
Methyl methanesulfonate	15	25	14	126	166	
		23	13	103	151	159*
Pyridine	2,000	90	87	68	25	
		79	85	53	22	24
	3,000	116	85	89	26	
		90	79	64	24	25
	4,000	72	75	86	40	
		88	79	145	55	47*
	5,000	82	70	73	30	
		89	67	79	30	30

TABLE F2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Pyridine

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+ S9						
Trial 1						
Medium		90	90	126	47	55
		79	104	124	53	
		83	102	137	55	
		74	105	141	64	
Methylcholanthrene ^d	2.5	50	18	820	552	556*
		43	20	726	561	
Pyridine	1,000	82	88	133	54	56
		89	96	152	57	
	2,000	94	77	230	82	68
		77	99	123	53	
	3,000	77	86	204	89	71
		89	80	140	52	
	4,000	100	70	167	55	59
		78	79	147	63	
	5,000	95	81	158	55	63
		98	73	207	70	
Trial 2						
Solvent control		85	101	111	43	52
		91	108	138	50	
		100	93	188	62	
		105	98	159	50	
Methylcholanthrene	2.5	54	24	686	421	436*
		58	28	791	451	
Pyridine	2,000	86	104	95	37	41
		87	108	119	46	
	3,000	78	101	87	37	43
		79	105	117	49	
	4,000	80	97	94	39	41
		84	91	107	42	
	5,000	109	78	101	31	33
		109	84	115	35	

* Positive response ($P \leq 0.05$) versus the solvent control

^a Study was performed at Inveresk Research International. The detailed protocol and these data are presented in McGregor *et al.* (1988).

^b Mutant fraction (MF) (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF/10⁶ cells treated).

^c Solvent control

^d Positive control

TABLE F3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Pyridine^a

Compound	Concentration ($\mu\text{g/mL}$)	Total Cells Scored	No. of Chromo- somes	No. of SCEs	SCEs/ Chromo- some	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome ^b (%)
S9								
Summary: Negative								
Distilled water ^c		50	1,049	415	0.39	8.3	26.0	
		50	1,049	424	0.40	8.5	31.0 ^e	
Mitomycin-C ^d	0.001	50	1,049	665	0.63	13.3	26.0	56.84
	0.004	10	208	201	0.96	20.1	26.0	139.08
Pyridine	167	50	1,043	407	0.39	8.1	26.0	3.46
	502	50	1,049	437	0.41	8.7	26.0	3.07
	1,673	50	1,050	434	0.41	8.7	31.0	2.26
	5,020	0						
P=0.273 ^f								
+S9								
Summary: Negative								
Distilled water		50	1,050	389	0.37	7.8	26.0	
Cyclophosphamide ^d	0.125	50	1,051	598	0.56	12.0	26.0	53.58
	0.5	10	207	186	0.89	18.6	26.0	142.54
Pyridine	502	50	1,048	416	0.39	8.3	26.0	7.14
	1,673	50	1,051	421	0.40	8.4	26.0	8.12
	5,020	50	1,051	388	0.36	7.8	26.0	0.35
P=0.494								

^a Study was performed at SITEK Research Laboratories. The detailed protocol is presented in Galloway *et al.* (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine

^b SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells

^c Solvent control

^d Positive control

^e Due to cell cycle delay, harvest time was extended to maximize the number of second-division metaphase cells available for analysis.

^f Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

TABLE F4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Pyridine^a

Compound	Concentration ($\mu\text{g/mL}$)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
S9					
Harvest time: 13.5 hours					
Summary: Negative					
Distilled water ^b		200	2	0.01	1.0
Mitomycin-C ^c	0.4	25	37	1.48	76.0
Pyridine	503	200	0	0.00	0.0
	1,081	200	0	0.00	0.0
	2,325	200	2	0.01	1.0
					P=0.450 ^d
+ S9					
Harvest time: 13.5 hours					
Summary: Negative					
Distilled water		200	2	0.01	1.0
Cyclophosphamide ^c	20	25	42	1.68	48.0
Pyridine	1,081	200	1	0.01	0.5
	2,325	200	1	0.01	0.5
	5,000	200	3	0.02	1.5
					P=0.305

^a Study was performed at SITEK Research Laboratories. The detailed protocol is presented in Galloway *et al.* (1987).

^b Solvent control

^c Positive control

^d Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

TABLE F5
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by Pyridine^a

Route of Exposure	Dose (ppm)	Incidence of Death (%)	Incidence of Sterility (%)	No. of Lethals/No. of X Chromosomes Tested			Total ^b
				Mating 1	Mating 2	Mating 3	
Study performed at Brown University ^c							
Feed	700 0	20	2	4/1,027 0/1,114	1/1,069 1/1,142	0/1,082 0/1,105	5/3,178 (0.16%) 1/3,361 (0.03%) P=0.043
Injection	7,000 0	5	0	1/1,770 1/2,170	1/2,281 2/2,750	3/2,039 0/1,379	5/6,090 (0.08%) 3/6,299 (0.05%) P=0.225
Feed	729 0	22	0	1/1,724 0/1,902	0/2,664 1/2,541	1/1,121 6/1,413	2/5,509 (0.04%) 7/5,856 (0.12%) P=0.943
Injection	500 0	4	0	4/1,916 2/1,908	1/2,006 1/1,933	2/1,944 0/1,921	7/5,866 (0.12%) 3/5,762 (0.05%) P=0.108
Study performed at University of Wisconsin, Madison ^d							
Feed	500 0	12	1	1/2,063 3/1,947	0/1,989 5/1,726	0/1,666 2/1,438	1/5,718 (0.02%) 10/5,111 (0.20%) P=0.998
Injection	4,300 0	26	9	7/1,854 3/4,163	1/1,731 2/3,949	1/1,608 1/3,285	9/5,193 (0.17%) 6/11,397 (0.05%) P=0.008

^a The mean mutant frequency from 518 negative control experiments is 0.074% (Mason *et al.*, 1992).

^b Total number of lethal mutations/total number of X chromosomes tested for three mating trials

^c The detailed protocol and these data are presented in Valencia *et al.* (1985) (first two exposures); data are not presented for the third and fourth exposures.

^d The detailed protocol and these data are presented in Mason *et al.* (1992).

TABLE F6
Induction of Reciprocal Translocations in *Drosophila melanogaster* by Pyridine^a

Route of Exposure	Dose (ppm)	Translocations/Total F ₁ Tested						No. of Tests	Total No. of Translocations	Total Translocations (%)
		1	2	3	4	5	6			
Injection	4,300	0/1,483	0/1,413	0/1,243	0/819	0/254	0/11	5,223	0	0
Historical control		0/27,245	0/31,611	0/22,410	2/23,623	0/10,506	0/768	116,163	2	0.002

^a Study was performed at University of Wisconsin, Madison. The detailed protocol and these data are presented in Mason *et al.* (1992). Results were not significant at the 5% level (Kastenbaum and Bowman, 1970).

TABLE F7
Induction of Chromosomal Aberrations in Mouse Bone Marrow Cells by Pyridine^a

Compound	Dose (mg/kg)	Total Cells Scored	Total Aberrations (gaps)	Cells with Aberrations ^b (%)
Trial 1				
Sample time: 17 hours				
Phosphate-buffered saline ^c		400	2	0.50 ± 0.33
Mitomycin-C ^d	1	400	11	2.25 ± 0.45
	2	400	48	9.50 ± 1.76
Pyridine	400	400	2	0.50 ± 0.50
	500	400	8	1.75 ± 0.59
	600	400	2	0.50 ± 0.33
				P=0.222 ^e
Trial 2				
Sample time: 36 hours				
Phosphate-buffered saline		400	6	1.50 ± 0.63
Mitomycin-C	1	400	14	3.00 ± 0.85
	2	400	68	6.25 ± 2.31
Pyridine	400	400	3	0.75 ± 0.53
	500	400	6	1.50 ± 0.82
	600	400	0	0.00 ± 0.00
				P=0.948

^a Study was performed at Environmental Health Research and Testing, Inc. Fifty first-division metaphase cells were scored from each of eight mice per group. The detailed protocol and these data are presented in McFee (1989).

^b Mean ± standard error

^c Solvent control

^d Positive control

^e Significance tested by the one-tailed trend test; significant at P≤0.05 (Margolin *et al.*, 1986)

TABLE F8
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Mice Treated with Pyridine by Intraperitoneal Injection^a

Compound	Dose (mg/kg)	Number of Mice	Micronucleated PCEs/ 1,000 PCEs ^b	PCEs ^b (%)
Phosphate-buffered saline ^c		5	1.60 ± 0.51	52.52 ± 4.30
Cyclophosphamide ^d	15	5	11.50 ± 0.91	52.46 ± 1.71
Pyridine	31.25	5	1.40 ± 0.29	52.22 ± 1.11
	62.5	5	1.60 ± 0.43	53.04 ± 3.89
	125	5	1.10 ± 0.51	51.40 ± 3.66
	250	5	1.10 ± 0.37	51.22 ± 1.61
	500	5	1.20 ± 0.25	48.02 ± 1.88
			P=0.811 ^e	

^a Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol and these data are presented in Shelby *et al.* (1993).

^b Mean ± standard error

^c Solvent control

^d Positive control

^e Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at $P \leq 0.025$ (Margolin *et al.*, 1990)

APPENDIX G
HEMATOLOGY AND CLINICAL CHEMISTRY
RESULTS

TABLE G1	Hematology and Clinical Chemistry Data for F344/N Rats	
	in the 13-Week Drinking Water Study of Pyridine	G-2
TABLE G2	Hematology and Clinical Chemistry Data for Male Wistar Rats	
	in the 13-Week Drinking Water Study of Pyridine	G-7

TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine^a

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Male						
Hematology						
n						
Day 5	10	9	10	10	10	10
Day 20	10	10	10	10	10	9
Week 13	10	10	10	10	10	10
Automated hematocrit (%)						
Day 5	46.8 ± 0.3	47.3 ± 0.5	48.1 ± 0.4*	47.9 ± 0.5*	47.9 ± 0.5	49.6 ± 0.4**
Day 20	49.6 ± 0.4	50.4 ± 0.3	48.2 ± 0.6	47.9 ± 0.3**	47.8 ± 0.4**	45.0 ± 0.4**
Week 13	46.9 ± 0.5	46.4 ± 0.3	46.8 ± 0.2	46.1 ± 0.3	45.9 ± 0.3	44.4 ± 0.7**
Manual hematocrit (%)						
Day 5	44.2 ± 0.3	44.7 ± 0.6	45.2 ± 0.3*	45.4 ± 0.5	45.5 ± 0.6	46.5 ± 0.5**
Day 20	48.0 ± 0.3	49.1 ± 0.6	46.6 ± 0.5	46.3 ± 0.5	46.5 ± 0.5*	43.3 ± 0.5**
Week 13	45.7 ± 0.5	44.8 ± 0.4	45.6 ± 0.4	44.7 ± 0.2	44.3 ± 0.4*	42.7 ± 0.7**
Hemoglobin (g/dL)						
Day 5	15.3 ± 0.1	15.4 ± 0.1	15.6 ± 0.1	15.7 ± 0.1	15.8 ± 0.1**	16.0 ± 0.2**
Day 20	16.3 ± 0.2	16.6 ± 0.1	15.7 ± 0.2	15.6 ± 0.1**	15.7 ± 0.1*	14.8 ± 0.2**
Week 13	15.4 ± 0.2	15.2 ± 0.1	15.3 ± 0.1	15.0 ± 0.2	14.9 ± 0.1*	14.3 ± 0.2**
Erythrocytes (10 ⁶ /μL)						
Day 5	8.40 ± 0.07	8.41 ± 0.13	8.54 ± 0.08	8.54 ± 0.07	8.58 ± 0.10	8.79 ± 0.08**
Day 20	8.92 ± 0.07	9.07 ± 0.07	8.62 ± 0.11	8.62 ± 0.07*	8.66 ± 0.10	8.27 ± 0.13**
Week 13	9.09 ± 0.11	9.00 ± 0.07	9.12 ± 0.05	8.88 ± 0.07	8.87 ± 0.09	8.52 ± 0.20*
Reticulocytes (10 ⁶ /μL)						
Day 5	0.18 ± 0.03	0.26 ± 0.05	0.20 ± 0.01	0.15 ± 0.02	0.15 ± 0.01	0.15 ± 0.01
Day 20	0.18 ± 0.02	0.17 ± 0.02	0.18 ± 0.01	0.20 ± 0.01	0.19 ± 0.02	0.16 ± 0.01
Week 13	0.17 ± 0.01	0.18 ± 0.02	0.19 ± 0.02	0.19 ± 0.02	0.19 ± 0.01	0.19 ± 0.02
Nucleated erythrocytes (10 ³ /μL)						
Day 5	0.01 ± 0.01	0.04 ± 0.02	0.00 ± 0.00	0.02 ± 0.02	0.04 ± 0.02	0.00 ± 0.00
Day 20	0.00 ± 0.00	0.03 ± 0.02	0.01 ± 0.01	0.05 ± 0.02*	0.02 ± 0.01	0.03 ± 0.02
Week 13	0.02 ± 0.01	0.04 ± 0.02	0.03 ± 0.02	0.01 ± 0.01	0.01 ± 0.01	0.06 ± 0.02
Mean cell volume (fL)						
Day 5	55.8 ± 0.3	56.3 ± 0.4	56.4 ± 0.3	56.2 ± 0.3	55.9 ± 0.3	56.6 ± 0.2
Day 20	55.5 ± 0.2	55.5 ± 0.4	55.8 ± 0.3	55.5 ± 0.3	55.3 ± 0.4	54.6 ± 0.5
Week 13	51.6 ± 0.2	51.5 ± 0.2	51.4 ± 0.2	52.0 ± 0.3	51.8 ± 0.5	52.3 ± 0.7
Mean cell hemoglobin (pg)						
Day 5	18.3 ± 0.1	18.3 ± 0.1	18.3 ± 0.1	18.3 ± 0.1	18.5 ± 0.1	18.2 ± 0.1
Day 20	18.3 ± 0.1	18.3 ± 0.1	18.3 ± 0.1	18.1 ± 0.1	18.1 ± 0.1	17.9 ± 0.1*
Week 13	17.0 ± 0.1	16.9 ± 0.1	16.8 ± 0.1	16.8 ± 0.1	16.8 ± 0.2	16.9 ± 0.2
Mean cell hemoglobin concentration (g/dL)						
Day 5	32.8 ± 0.2	32.4 ± 0.1	32.5 ± 0.1	32.7 ± 0.1	33.1 ± 0.2	32.3 ± 0.2
Day 20	32.8 ± 0.2	33.0 ± 0.2	32.6 ± 0.2	32.7 ± 0.2	32.8 ± 0.2	32.9 ± 0.2
Week 13	32.8 ± 0.1	32.9 ± 0.1	32.7 ± 0.1	32.4 ± 0.2	32.5 ± 0.1*	32.3 ± 0.1**
Platelets (10 ³ /μL)						
Day 5	908.7 ± 26.6	973.1 ± 33.9	957.3 ± 23.1	924.4 ± 27.9	880.7 ± 21.4	937.0 ± 19.9
Day 20	856.9 ± 12.1	902.3 ± 31.3	880.4 ± 22.8	917.8 ± 15.1*	1,065.7 ± 39.8**	949.0 ± 28.2**
Week 13	731.0 ± 26.3	711.2 ± 12.1	732.3 ± 15.5	760.1 ± 15.5	791.8 ± 42.0*	869.5 ± 65.4*
Leukocytes (10 ³ /μL)						
Day 5	10.82 ± 0.44	11.72 ± 0.45	11.25 ± 0.43	10.36 ± 0.40	10.19 ± 0.45	10.82 ± 0.42
Day 20	9.31 ± 0.42	11.48 ± 0.49*	8.83 ± 0.22	9.32 ± 0.34	9.62 ± 0.51	9.42 ± 0.49
Week 13	9.46 ± 0.43	10.24 ± 0.31	9.93 ± 0.50	9.96 ± 0.37	10.24 ± 0.49	11.26 ± 0.56
Segmented neutrophils (10 ³ /μL)						
Day 5	1.84 ± 0.14	1.66 ± 0.13	1.47 ± 0.16	1.60 ± 0.13	1.45 ± 0.13	1.77 ± 0.23
Day 20	1.45 ± 0.15	1.68 ± 0.17	1.08 ± 0.13	1.28 ± 0.10	1.54 ± 0.22	1.00 ± 0.09
Week 13	2.01 ± 0.20	1.84 ± 0.14	1.64 ± 0.21	1.78 ± 0.23	1.90 ± 0.16	2.16 ± 0.29

TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Male (continued)						
Hematology (continued)						
n						
Day 5	10	9	10	10	10	10
Day 20	10	10	10	10	10	9
Week 13	10	10	10	10	10	10
Lymphocytes ($10^3/\mu\text{L}$)						
Day 5	8.84 \pm 0.39	9.95 \pm 0.44	9.73 \pm 0.46	8.61 \pm 0.36	8.66 \pm 0.39	9.02 \pm 0.34
Day 20	7.80 \pm 0.32	9.73 \pm 0.49*	7.68 \pm 0.27	8.00 \pm 0.37	7.99 \pm 0.48	8.32 \pm 0.45
Week 13	7.40 \pm 0.37	8.37 \pm 0.28	8.25 \pm 0.48	8.15 \pm 0.41	8.27 \pm 0.51	9.03 \pm 0.44*
Monocytes ($10^3/\mu\text{L}$)						
Day 5	0.11 \pm 0.04	0.05 \pm 0.02	0.05 \pm 0.02	0.09 \pm 0.04	0.05 \pm 0.02	0.01 \pm 0.01
Day 20	0.05 \pm 0.02	0.03 \pm 0.02	0.04 \pm 0.02	0.01 \pm 0.01	0.03 \pm 0.01	0.06 \pm 0.02
Week 13	0.02 \pm 0.01	0.01 \pm 0.01	0.02 \pm 0.01	0.01 \pm 0.01	0.03 \pm 0.02	0.05 \pm 0.04
Basophils ($10^3/\mu\text{L}$)						
Day 5	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000
Day 20	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000
Week 13	0.000 \pm 0.000	0.011 \pm 0.011	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000
Eosinophils ($10^3/\mu\text{L}$)						
Day 5	0.02 \pm 0.01	0.06 \pm 0.03	0.01 \pm 0.01	0.06 \pm 0.03	0.03 \pm 0.02	0.03 \pm 0.02
Day 20	0.01 \pm 0.01	0.04 \pm 0.02	0.04 \pm 0.01	0.03 \pm 0.02	0.06 \pm 0.02	0.04 \pm 0.02
Week 13	0.02 \pm 0.02	0.01 \pm 0.01	0.02 \pm 0.01	0.02 \pm 0.02	0.05 \pm 0.02	0.02 \pm 0.01
Clinical Chemistry						
n						
Day 5	10	10	10	10	10	10
Day 20	10	10	10	10	10	9
Week 13	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 5	23.1 \pm 0.7	24.1 \pm 0.8	25.5 \pm 0.7	25.9 \pm 0.9	24.1 \pm 0.8	23.8 \pm 0.8
Day 20	24.3 \pm 0.6	22.8 \pm 0.6	23.9 \pm 0.5	24.8 \pm 0.4	23.2 \pm 0.5	25.0 \pm 0.5
Week 13	25.1 \pm 0.4	23.1 \pm 0.7	23.9 \pm 0.6	23.9 \pm 0.7	25.0 \pm 1.0	25.3 \pm 1.1
Creatinine (mg/dL)						
Day 5	0.49 \pm 0.01	0.51 \pm 0.02	0.53 \pm 0.02	0.49 \pm 0.01	0.51 \pm 0.01	0.50 \pm 0.01
Day 20	0.61 \pm 0.03	0.56 \pm 0.03	0.59 \pm 0.02	0.60 \pm 0.02	0.60 \pm 0.03	0.61 \pm 0.02
Week 13	0.59 \pm 0.02	0.55 \pm 0.03	0.60 \pm 0.03	0.60 \pm 0.04	0.59 \pm 0.03	0.64 \pm 0.03
Total protein (g/dL)						
Day 5	6.3 \pm 0.1	6.4 \pm 0.1	6.6 \pm 0.1	6.5 \pm 0.1	6.4 \pm 0.1	6.3 \pm 0.1
Day 20	6.8 \pm 0.1	7.0 \pm 0.1	7.1 \pm 0.1	7.1 \pm 0.1	7.1 \pm 0.1	7.1 \pm 0.1
Week 13	6.4 \pm 0.1	6.5 \pm 0.1	6.8 \pm 0.1*	6.9 \pm 0.1**	7.1 \pm 0.1**	6.8 \pm 0.1**
Albumin (g/dL)						
Day 5	3.5 \pm 0.1	3.6 \pm 0.1	3.8 \pm 0.1*	3.7 \pm 0.1*	3.6 \pm 0.1	3.6 \pm 0.1
Day 20	3.8 \pm 0.1	4.0 \pm 0.1	4.0 \pm 0.1	4.0 \pm 0.1	4.1 \pm 0.1**	3.9 \pm 0.1
Week 13	3.5 \pm 0.1	3.6 \pm 0.1	3.9 \pm 0.1**	3.8 \pm 0.0**	4.0 \pm 0.0**	3.9 \pm 0.1**
Alanine aminotransferase (IU/L)						
Day 5	42 \pm 2	46 \pm 1	51 \pm 1**	47 \pm 1	60 \pm 11	46 \pm 1
Day 20	53 \pm 3	44 \pm 3	40 \pm 1*	39 \pm 2**	49 \pm 6	54 \pm 6
Week 13	60 \pm 2	56 \pm 4	52 \pm 5	44 \pm 2*	50 \pm 3	583 \pm 268
Alkaline phosphatase (IU/L)						
Day 5	441 \pm 15	468 \pm 8	454 \pm 16	423 \pm 9	465 \pm 10	456 \pm 10
Day 20	411 \pm 11	302 \pm 12**	385 \pm 14**	320 \pm 14**	275 \pm 21**	331 \pm 10**
Week 13	236 \pm 6	219 \pm 4	223 \pm 6	203 \pm 3*	176 \pm 8**	278 \pm 25

TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Male (continued)						
Clinical Chemistry (continued)						
n						
Day 5	10	10	10	10	10	10
Day 20	10	10	10	10	10	9
Week 13	10	10	10	10	10	10
Creatine kinase (U/L)						
Day 5	275 ± 63	260 ± 66	262 ± 43	183 ± 17	244 ± 33 ^b	193 ± 21
Day 20	169 ± 14 ^b	241 ± 31 ^b	167 ± 14	198 ± 20	180 ± 20	171 ± 28
Week 13	234 ± 62	243 ± 63	223 ± 58	202 ± 56	339 ± 115	161 ± 32 ^b
Sorbitol dehydrogenase (IU/L)						
Day 5	8 ± 0	9 ± 0	10 ± 1*	9 ± 1	27 ± 17	11 ± 0**
Day 20	10 ± 0	8 ± 0	10 ± 1	10 ± 1	39 ± 13	23 ± 7
Week 13	12 ± 1	11 ± 1	10 ± 1	10 ± 1	12 ± 1	395 ± 217
Bile acids (μmol/L)						
Day 5	33.5 ± 4.0	34.7 ± 3.5	38.6 ± 7.5	26.6 ± 1.7	45.9 ± 7.3	40.6 ± 5.1
Day 20	28.3 ± 3.2	40.3 ± 3.7*	26.6 ± 3.7	30.3 ± 2.7	61.0 ± 6.1**	59.6 ± 7.6**
Week 13	30.5 ± 4.7	29.5 ± 4.2	26.0 ± 3.9	40.3 ± 7.7	62.1 ± 12.9*	150.0 ± 19.7**
Female						
n						
Day 5	10	10	10	10	10	10
Day 20	10	10	10	10	10	10
Week 13	10	10	10	10	10	8
Hematology						
Automated hematocrit (%)						
Day 5	48.4 ± 0.5	48.9 ± 0.5	50.3 ± 0.6	48.6 ± 0.6	50.7 ± 0.7	50.5 ± 1.0
Day 20	48.2 ± 0.4	47.4 ± 0.5	47.8 ± 0.3	47.0 ± 0.5	45.5 ± 0.6**	48.2 ± 1.0
Week 13	46.5 ± 0.3	45.4 ± 0.3*	45.5 ± 0.3*	43.5 ± 0.5**	43.1 ± 0.3**	43.8 ± 0.4**
Manual hematocrit (%)						
Day 5	44.9 ± 0.7	45.5 ± 0.4	46.9 ± 0.4	45.5 ± 0.6	46.9 ± 0.5	47.0 ± 0.9
Day 20	46.7 ± 0.3	45.8 ± 0.6	46.3 ± 0.2	45.5 ± 0.4	44.4 ± 0.6*	47.4 ± 0.9
Week 13	44.8 ± 0.3	44.0 ± 0.3	44.0 ± 0.4	41.3 ± 0.8**	40.9 ± 0.4**	41.5 ± 0.5**
Hemoglobin (g/dL)						
Day 5	16.0 ± 0.1	16.0 ± 0.2	16.4 ± 0.1	15.9 ± 0.2	16.6 ± 0.2	16.5 ± 0.3
Day 20	16.6 ± 0.2	16.3 ± 0.1	16.3 ± 0.1	15.8 ± 0.1**	15.6 ± 0.2**	16.2 ± 0.3**
Week 13	15.8 ± 0.1	15.3 ± 0.1**	15.2 ± 0.1**	14.4 ± 0.2**	14.2 ± 0.1**	14.3 ± 0.1**
Erythrocytes (10 ⁶ /μL)						
Day 5	7.96 ± 0.07	7.97 ± 0.11	8.19 ± 0.11	7.86 ± 0.09	8.30 ± 0.11	8.18 ± 0.21
Day 20	8.25 ± 0.09	8.06 ± 0.08	8.14 ± 0.07	7.92 ± 0.10	7.85 ± 0.09	8.43 ± 0.18
Week 13	8.66 ± 0.06	8.43 ± 0.04**	8.40 ± 0.11*	7.94 ± 0.11**	7.93 ± 0.10**	8.17 ± 0.11**
Reticulocytes (10 ⁶ /μL)						
Day 5	0.18 ± 0.02	0.17 ± 0.01	0.18 ± 0.02	0.13 ± 0.01	0.19 ± 0.02	0.16 ± 0.01
Day 20	0.16 ± 0.01	0.16 ± 0.02	0.16 ± 0.01	0.18 ± 0.01	0.17 ± 0.02	0.17 ± 0.01
Week 13	0.15 ± 0.01	0.15 ± 0.01	0.15 ± 0.01	0.15 ± 0.01	0.15 ± 0.01	0.17 ± 0.01
Nucleated erythrocytes (10 ³ /μL)						
Day 5	0.03 ± 0.03	0.05 ± 0.02	0.04 ± 0.03	0.06 ± 0.02	0.04 ± 0.02	0.04 ± 0.03
Day 20	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Week 13	0.00 ± 0.00	0.00 ± 0.00	0.03 ± 0.01	0.03 ± 0.02	0.01 ± 0.01	0.00 ± 0.00

TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Female (continued)						
n						
Day 5	10	10	10	10	10	10
Day 20	10	10	10	10	10	10
Week 13	10	10	10	10	10	8
Hematology (continued)						
Mean cell volume (fL)						
Day 5	60.9 ± 0.4	61.6 ± 0.5	61.6 ± 0.3	61.7 ± 0.4	61.3 ± 0.3	61.7 ± 0.7
Day 20	58.4 ± 0.4	58.7 ± 0.3	58.7 ± 0.3	59.4 ± 0.5	58.0 ± 0.3	57.3 ± 0.4
Week 13	53.7 ± 0.2	54.0 ± 0.1	54.2 ± 0.6	54.2 ± 0.2	54.4 ± 0.4	53.6 ± 0.3
Mean cell hemoglobin (pg)						
Day 5	20.1 ± 0.2	20.1 ± 0.2	20.1 ± 0.2	20.2 ± 0.2	20.0 ± 0.1	20.2 ± 0.2 ^b
Day 20	20.1 ± 0.1	20.2 ± 0.1	20.0 ± 0.1	19.9 ± 0.1	19.8 ± 0.1	19.3 ± 0.1**
Week 13	18.2 ± 0.1	18.1 ± 0.1	18.2 ± 0.2	18.2 ± 0.2	18.0 ± 0.2**	17.5 ± 0.2**
Mean cell hemoglobin concentration (g/dL)						
Day 5	33.1 ± 0.2	32.7 ± 0.1	32.7 ± 0.3	32.7 ± 0.3	32.7 ± 0.2	32.7 ± 0.2
Day 20	34.4 ± 0.2	34.4 ± 0.2	34.0 ± 0.2	33.7 ± 0.2	34.2 ± 0.3	33.7 ± 0.2*
Week 13	34.0 ± 0.1	33.7 ± 0.2	33.5 ± 0.1*	33.1 ± 0.2**	33.0 ± 0.1**	32.7 ± 0.2**
Platelets (10 ³ /μL)						
Day 5	941.7 ± 30.3	885.4 ± 26.5	971.4 ± 26.3	906.8 ± 11.8 ^b	863.3 ± 21.2	857.5 ± 61.5
Day 20	930.8 ± 22.3	885.0 ± 28.0	884.6 ± 44.3	982.5 ± 23.9	919.7 ± 16.9	812.6 ± 61.7
Week 13	721.5 ± 17.2	741.0 ± 9.5	729.4 ± 32.6	738.5 ± 38.4	759.2 ± 36.4	751.3 ± 45.7
Leukocytes (10 ³ /μL)						
Day 5	10.19 ± 0.41	9.35 ± 0.34	8.84 ± 0.35	8.67 ± 0.26	8.97 ± 0.50	8.36 ± 0.56*
Day 20	9.54 ± 0.29	9.60 ± 0.34	9.15 ± 0.42	9.41 ± 0.32	9.05 ± 0.35	8.95 ± 0.43
Week 13	8.01 ± 0.32	8.38 ± 0.18	8.35 ± 0.23	7.93 ± 0.47	8.89 ± 0.28	8.70 ± 0.49
Segmented neutrophils (10 ³ /μL)						
Day 5	1.18 ± 0.18	1.48 ± 0.22	1.17 ± 0.13	0.98 ± 0.12	1.20 ± 0.23	1.15 ± 0.17
Day 20	1.31 ± 0.14	1.49 ± 0.19	1.32 ± 0.13	1.44 ± 0.17	1.41 ± 0.17	1.87 ± 0.25
Week 13	1.55 ± 0.15	1.48 ± 0.18	1.42 ± 0.09	1.39 ± 0.14	1.62 ± 0.19	1.27 ± 0.16
Lymphocytes (10 ³ /μL)						
Day 5	8.89 ± 0.42	7.81 ± 0.43	7.61 ± 0.41	7.64 ± 0.28	7.93 ± 0.52	7.14 ± 0.62
Day 20	8.18 ± 0.32	8.06 ± 0.42	7.75 ± 0.46	7.82 ± 0.26	7.54 ± 0.36	6.99 ± 0.48
Week 13	6.41 ± 0.23	6.87 ± 0.23	6.86 ± 0.24	6.42 ± 0.41	7.20 ± 0.28	7.40 ± 0.48
Monocytes (10 ³ /μL)						
Day 5	0.11 ± 0.04	0.03 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.04 ± 0.01	0.03 ± 0.01
Day 20	0.05 ± 0.02	0.04 ± 0.03	0.04 ± 0.02	0.11 ± 0.03	0.08 ± 0.04	0.07 ± 0.04
Week 13	0.04 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.04 ± 0.02	0.04 ± 0.02	0.01 ± 0.01
Basophils (10 ³ /μL)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 20	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 13	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10 ³ /μL)						
Day 5	0.01 ± 0.01	0.03 ± 0.02	0.03 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.05 ± 0.03
Day 20	0.01 ± 0.01	0.01 ± 0.01	0.04 ± 0.03	0.04 ± 0.02	0.02 ± 0.01	0.03 ± 0.02
Week 13	0.02 ± 0.01	0.03 ± 0.01	0.04 ± 0.02	0.05 ± 0.02	0.04 ± 0.01	0.03 ± 0.02

TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Female (continued)						
n						
Day 5	10	10	10	10	10	10
Day 20	10	10	10	10	10	10
Week 13	10	10	10	10	10	8
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 5	20.9 ± 1.0	21.2 ± 2.0	20.6 ± 0.8	20.3 ± 1.0	24.0 ± 1.0	22.9 ± 0.7
Day 20	21.5 ± 0.7	22.0 ± 1.3	22.1 ± 1.1	22.6 ± 0.6	22.0 ± 0.6	25.9 ± 1.4
Week 13	21.0 ± 0.8	20.4 ± 0.8	21.5 ± 1.2	18.3 ± 0.6	19.8 ± 0.7	23.4 ± 1.3
Creatinine (mg/dL)						
Day 5	0.55 ± 0.02	0.55 ± 0.03	0.51 ± 0.01	0.52 ± 0.03	0.58 ± 0.01	0.56 ± 0.02
Day 20	0.58 ± 0.02	0.56 ± 0.03	0.61 ± 0.02	0.56 ± 0.03	0.57 ± 0.02	0.59 ± 0.02 ^b
Week 13	0.62 ± 0.02	0.60 ± 0.01	0.63 ± 0.03	0.61 ± 0.02	0.60 ± 0.03	0.61 ± 0.05
Total protein (g/dL)						
Day 5	6.0 ± 0.1	6.2 ± 0.1	6.7 ± 0.0**	6.2 ± 0.1	6.5 ± 0.1**	6.0 ± 0.1
Day 20	6.4 ± 0.1	6.6 ± 0.1	6.5 ± 0.1	6.8 ± 0.1*	6.9 ± 0.1**	6.8 ± 0.1**
Week 13	6.8 ± 0.1	6.6 ± 0.1	6.7 ± 0.1	6.8 ± 0.1	7.0 ± 0.1	6.7 ± 0.1
Albumin (g/dL)						
Day 5	3.7 ± 0.0	3.7 ± 0.1	4.0 ± 0.1**	3.7 ± 0.1	3.9 ± 0.1*	3.8 ± 0.1
Day 20	3.5 ± 0.1	3.6 ± 0.1	3.7 ± 0.1	3.8 ± 0.1**	4.1 ± 0.1**	4.0 ± 0.1**
Week 13	3.9 ± 0.1	3.9 ± 0.0	4.0 ± 0.1	4.0 ± 0.1	4.0 ± 0.1	4.0 ± 0.1
Alanine aminotransferase (IU/L)						
Day 5	36 ± 1	34 ± 1	33 ± 1	35 ± 2	45 ± 5	432 ± 294
Day 20	35 ± 1	33 ± 2	30 ± 1	28 ± 1*	29 ± 2*	1,295 ± 1,133
Week 13	40 ± 1	31 ± 2**	33 ± 2*	30 ± 1**	30 ± 1**	141 ± 72
Alkaline phosphatase (IU/L)						
Day 5	419 ± 7	375 ± 11*	367 ± 7**	368 ± 8**	405 ± 10	410 ± 12
Day 20	357 ± 8	328 ± 5**	315 ± 7**	287 ± 3**	283 ± 6**	314 ± 18**
Week 13	210 ± 5	193 ± 5	176 ± 4**	162 ± 7**	168 ± 5**	209 ± 17**
Creatine kinase (IU/L)						
Day 5	195 ± 28	230 ± 43	257 ± 22	207 ± 21 ^b	300 ± 27**	288 ± 39*
Day 20	266 ± 74	222 ± 53	208 ± 45	175 ± 38	143 ± 9	144 ± 15 ^b
Week 13	169 ± 23	119 ± 19	187 ± 42	210 ± 40	159 ± 20	240 ± 70
Sorbitol dehydrogenase (IU/L)						
Day 5	8 ± 1	7 ± 0	6 ± 1	7 ± 0	39 ± 20	111 ± 91
Day 20	8 ± 1	9 ± 1	10 ± 0	10 ± 0	17 ± 6**	383 ± 162** ^b
Week 13	8 ± 0	9 ± 0	8 ± 1	9 ± 1	10 ± 1	289 ± 204**
Bile acids (μmol/L)						
Day 5	32.3 ± 3.4	28.3 ± 5.1	20.9 ± 2.8	43.0 ± 5.9	39.3 ± 11.2	69.2 ± 25.7
Day 20	34.1 ± 3.9	37.0 ± 5.9	41.1 ± 6.1	40.0 ± 8.9	55.0 ± 4.9*	202.0 ± 114.1**
Week 13	47.3 ± 9.8	39.5 ± 4.9	38.0 ± 5.6	38.9 ± 4.6	54.5 ± 7.9	87.3 ± 21.8

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test

** $P \leq 0.01$

^a Mean ± standard error. Statistical tests were performed on unrounded data.

^b n=9

TABLE G2
Hematology and Clinical Chemistry Data for Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine^a

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Hematology						
n						
Day 5	10	10	10	10	10	10
Day 20	10	9	9	9	10	10
Week 13	10	10	10	10	9	10
Automated hematocrit (%)						
Day 5	40.7 ± 0.4	40.1 ± 0.7	41.0 ± 0.5	41.5 ± 0.6	45.6 ± 0.7**	45.0 ± 1.0**
Day 20	43.0 ± 0.5	43.0 ± 0.7	42.6 ± 0.8	43.1 ± 0.5	42.9 ± 0.3	44.2 ± 0.9
Week 13	45.0 ± 0.5	45.3 ± 0.7	45.4 ± 0.3	46.2 ± 0.7	46.0 ± 0.3	44.6 ± 0.7
Manual hematocrit (%)						
Day 5	39.3 ± 0.4	38.6 ± 0.9	39.8 ± 0.5	40.1 ± 0.7	44.2 ± 0.8**	43.4 ± 1.0**
Day 20	41.3 ± 0.6	42.7 ± 0.7	41.8 ± 0.8	42.2 ± 0.5	41.3 ± 0.4	43.5 ± 1.0
Week 13	43.5 ± 0.6	44.0 ± 0.6	44.2 ± 0.2	44.7 ± 0.6	44.4 ± 0.4	43.4 ± 0.6
Hemoglobin (g/dL)						
Day 5	13.3 ± 0.1	13.1 ± 0.2	13.5 ± 0.2	13.7 ± 0.2	15.1 ± 0.2**	14.8 ± 0.3**
Day 20	14.3 ± 0.2	14.2 ± 0.2	14.0 ± 0.2	14.1 ± 0.2	14.0 ± 0.1	14.6 ± 0.3
Week 13	15.1 ± 0.2	15.2 ± 0.2	15.2 ± 0.1	15.5 ± 0.1	15.3 ± 0.1	14.8 ± 0.2
Erythrocytes (10 ⁶ /μL)						
Day 5	6.43 ± 0.07	6.35 ± 0.10	6.43 ± 0.09	6.62 ± 0.08	7.34 ± 0.16**	7.13 ± 0.17**
Day 20	6.99 ± 0.12	6.94 ± 0.10	6.90 ± 0.12	7.04 ± 0.10	7.07 ± 0.09	7.36 ± 0.13
Week 13	8.52 ± 0.14	8.59 ± 0.17	8.71 ± 0.12	8.61 ± 0.14	8.64 ± 0.12	8.42 ± 0.10
Reticulocytes (10 ⁶ /μL)						
Day 5	0.27 ± 0.02	0.29 ± 0.03	0.29 ± 0.02	0.32 ± 0.02	0.27 ± 0.02	0.26 ± 0.02
Day 20	0.21 ± 0.01	0.21 ± 0.01	0.18 ± 0.01	0.19 ± 0.01	0.22 ± 0.02	0.23 ± 0.01
Week 13	0.13 ± 0.01	0.15 ± 0.01	0.14 ± 0.01	0.16 ± 0.01	0.18 ± 0.02	0.15 ± 0.01
Nucleated erythrocytes (10 ³ /μL)						
Day 5	0.06 ± 0.02	0.02 ± 0.01	0.04 ± 0.02	0.01 ± 0.01*	0.02 ± 0.01	0.02 ± 0.01
Day 20	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.03 ± 0.02	0.03 ± 0.02	0.01 ± 0.01
Week 13	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.03 ± 0.02	0.04 ± 0.02
Mean cell volume (fL)						
Day 5	63.5 ± 0.6	63.2 ± 0.7	63.9 ± 0.7	62.6 ± 0.6	62.2 ± 0.5	63.2 ± 0.7
Day 20	61.7 ± 0.7	62.1 ± 0.9	61.8 ± 0.7	61.4 ± 0.6	60.7 ± 0.4	60.3 ± 0.5
Week 13	52.9 ± 0.6	52.9 ± 0.5	52.4 ± 0.5	53.8 ± 0.6	53.3 ± 0.7	53.2 ± 0.5
Mean cell hemoglobin (pg)						
Day 5	20.8 ± 0.2	20.7 ± 0.2	21.0 ± 0.2	20.6 ± 0.2	20.6 ± 0.2	20.8 ± 0.2
Day 20	20.4 ± 0.2	20.5 ± 0.2	20.4 ± 0.2	20.1 ± 0.2	19.8 ± 0.2	19.8 ± 0.2*
Week 13	17.7 ± 0.3	17.7 ± 0.2	17.5 ± 0.2	18.0 ± 0.2	17.7 ± 0.2	17.6 ± 0.2
Mean cell hemoglobin concentration (g/dL)						
Day 5	32.8 ± 0.1	32.7 ± 0.1	32.9 ± 0.2	32.9 ± 0.2	33.1 ± 0.2	32.9 ± 0.1
Day 20	33.2 ± 0.2	33.1 ± 0.3	33.0 ± 0.2	32.8 ± 0.2	32.7 ± 0.1	33.0 ± 0.1
Week 13	33.5 ± 0.2	33.6 ± 0.1	33.5 ± 0.2	33.5 ± 0.2	33.3 ± 0.2	33.3 ± 0.1
Platelets (10 ³ /μL)						
Day 5	1,356.5 ± 55.6	1,361.6 ± 46.8	1,398.8 ± 66.0	1,297.1 ± 70.9	1,364.3 ± 50.5	1,421.5 ± 75.1
Day 20	1,227.3 ± 39.0	1,227.0 ± 49.9	1,225.9 ± 46.1	1,177.4 ± 67.6	1,207.3 ± 52.1	1,258.0 ± 78.4
Week 13	1,055.2 ± 89.2	993.1 ± 57.2	1,012.2 ± 53.8	1,040.8 ± 55.8	1,232.1 ± 62.4	1,047.6 ± 72.7
Leukocytes (10 ³ /μL)						
Day 5	9.82 ± 0.56	11.44 ± 0.45	9.11 ± 0.94	9.29 ± 0.61	8.98 ± 0.32	9.05 ± 0.84
Day 20	10.09 ± 0.61	12.41 ± 0.53	10.14 ± 0.87	9.52 ± 0.35	10.16 ± 0.78	11.15 ± 0.92
Week 13	9.81 ± 0.77	10.67 ± 0.88	9.89 ± 0.61	10.45 ± 0.43	11.38 ± 0.47	10.81 ± 0.87
Segmented neutrophils (10 ³ /μL)						
Day 5	1.34 ± 0.17	1.98 ± 0.27	1.39 ± 0.21	1.47 ± 0.20	1.52 ± 0.14	1.26 ± 0.16
Day 20	1.46 ± 0.19	1.84 ± 0.24	1.54 ± 0.14	1.29 ± 0.17	1.55 ± 0.15	2.02 ± 0.34
Week 13	1.66 ± 0.17	1.52 ± 0.16	1.55 ± 0.21	1.71 ± 0.14	2.08 ± 0.19	1.67 ± 0.21
Lymphocytes (10 ³ /μL)						
Day 5	8.41 ± 0.49	9.32 ± 0.35	7.64 ± 0.78	7.70 ± 0.51	7.38 ± 0.34	7.69 ± 0.86
Day 20	8.52 ± 0.60	10.48 ± 0.62	8.51 ± 0.80	8.13 ± 0.37	8.50 ± 0.66	9.01 ± 0.74
Week 13	8.06 ± 0.72	9.06 ± 0.79	8.24 ± 0.70	8.63 ± 0.42	9.19 ± 0.50	9.05 ± 0.81

TABLE G2
Hematology and Clinical Chemistry Data for Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Hematology (continued)						
n						
Day 5	10	10	10	10	10	10
Day 20	10	9	9	9	10	10
Week 13	10	10	10	10	9	10
Monocytes ($10^3/\mu\text{L}$)						
Day 5	0.04 ± 0.02	0.08 ± 0.03	0.05 ± 0.03	0.09 ± 0.03	0.03 ± 0.01	0.04 ± 0.02
Day 20	0.08 ± 0.03	0.08 ± 0.03	0.07 ± 0.02	0.07 ± 0.02	0.05 ± 0.02	0.09 ± 0.02
Week 13	0.03 ± 0.02	0.05 ± 0.03	0.03 ± 0.02	0.03 ± 0.02	0.06 ± 0.03	0.07 ± 0.02
Basophils ($10^3/\mu\text{L}$)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 20	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 13	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils ($10^3/\mu\text{L}$)						
Day 5	0.03 ± 0.02	0.06 ± 0.03	0.03 ± 0.02	0.03 ± 0.03	0.05 ± 0.02	0.06 ± 0.03
Day 20	0.03 ± 0.02	0.01 ± 0.01	0.03 ± 0.02	0.03 ± 0.02	0.06 ± 0.03	0.04 ± 0.02
Week 13	0.06 ± 0.02	0.05 ± 0.02	0.07 ± 0.03	0.09 ± 0.04	0.05 ± 0.03	0.02 ± 0.01
Clinical Chemistry						
n						
Day 5	10	10	10	10	10	10
Day 20	10	10	10	10	10	10
Week 13	10	10	10	10	9	10
Urea nitrogen (mg/dL)						
Day 5	19.9 ± 0.8	19.4 ± 0.6	18.4 ± 1.0	18.9 ± 1.0	23.1 ± 1.1*	25.2 ± 1.3**
Day 20	23.3 ± 0.9	24.5 ± 0.5	22.7 ± 0.6	25.6 ± 1.0	25.8 ± 0.6*	28.0 ± 1.1**
Week 13	28.1 ± 0.8	27.5 ± 0.9	27.0 ± 1.0	26.8 ± 1.7	31.2 ± 1.8	29.7 ± 2.3
Creatinine (mg/dL)						
Day 5	0.50 ± 0.03	0.52 ± 0.02	0.46 ± 0.02	0.48 ± 0.02	0.53 ± 0.03	0.52 ± 0.01
Day 20	0.54 ± 0.02	0.53 ± 0.02	0.54 ± 0.02	0.53 ± 0.05	0.57 ± 0.02	0.57 ± 0.04
Week 13	0.62 ± 0.04	0.68 ± 0.02	0.68 ± 0.02	0.72 ± 0.03	0.74 ± 0.04	0.67 ± 0.03
Total protein (g/dL)						
Day 5	5.9 ± 0.1	5.8 ± 0.1	5.8 ± 0.1	5.9 ± 0.1	5.8 ± 0.1	6.1 ± 0.2
Day 20	6.5 ± 0.1	6.7 ± 0.1	6.4 ± 0.1	6.8 ± 0.1	6.7 ± 0.1	6.7 ± 0.1
Week 13	6.6 ± 0.1	6.7 ± 0.1	6.7 ± 0.1	7.0 ± 0.1	6.9 ± 0.1	6.6 ± 0.1
Albumin (g/dL)						
Day 5	3.0 ± 0.0	3.2 ± 0.1	3.1 ± 0.0	3.2 ± 0.1	3.2 ± 0.1	3.3 ± 0.1*
Day 20	3.3 ± 0.1	3.4 ± 0.1	3.3 ± 0.1	3.5 ± 0.0	3.4 ± 0.1	3.4 ± 0.1
Week 13	3.6 ± 0.1	3.8 ± 0.1	3.8 ± 0.1	3.9 ± 0.1*	3.8 ± 0.1	3.8 ± 0.1
Alanine aminotransferase (IU/L)						
Day 5	52 ± 2	53 ± 2	52 ± 2	53 ± 4	117 ± 30**	134 ± 74
Day 20	48 ± 2	43 ± 1	45 ± 2	45 ± 2	45 ± 2	299 ± 162
Week 13	54 ± 2	51 ± 4	50 ± 3	47 ± 3	146 ± 51	62 ± 11
Alkaline phosphatase (IU/L)						
Day 5	339 ± 13	343 ± 19	327 ± 20	303 ± 26	339 ± 29	378 ± 30
Day 20	294 ± 11	281 ± 21	268 ± 16	229 ± 16*	262 ± 19	288 ± 30
Week 13	179 ± 7	189 ± 8	160 ± 7	157 ± 6*	168 ± 18	143 ± 11*
Creatine kinase (U/L)						
Day 5	242 ± 23	211 ± 22	280 ± 31	255 ± 21	306 ± 35	291 ± 51
Day 20	223 ± 42	322 ± 69	345 ± 80	298 ± 56	333 ± 91	362 ± 99
Week 13	274 ± 65	454 ± 136	290 ± 45	272 ± 58	331 ± 64	309 ± 56

TABLE G2
Hematology and Clinical Chemistry Data for Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Clinical Chemistry (continued)						
n						
Day 5	10	10	10	10	10	10
Day 20	10	10	10	10	10	10
Week 13	10	10	10	10	9	10
Sorbitol dehydrogenase (IU/L)						
Day 5	8 ± 1	8 ± 1	7 ± 1	7 ± 0	615 ± 179**	370 ± 289**
Day 20	7 ± 0	7 ± 1	7 ± 1	8 ± 1	9 ± 1	1,075 ± 605**
Week 13	7 ± 0	8 ± 1	7 ± 1	9 ± 1	253 ± 94**	49 ± 29**
Bile acids (μmol/L)						
Day 5	100.0 ± 14.8	77.4 ± 8.4	118.5 ± 12.6	119.1 ± 16.9	235.0 ± 44.4**	191.3 ± 27.9**
Day 20	70.2 ± 8.1	76.0 ± 8.4	98.0 ± 14.9	159.1 ± 41.2*	111.5 ± 23.3	172.4 ± 37.9*
Week 13	75.5 ± 13.9	66.7 ± 6.7	67.4 ± 6.3	64.1 ± 8.1	117.8 ± 24.9	116.3 ± 20.2

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test

** $P \leq 0.01$

^a Mean ± standard error. Statistical tests were performed on unrounded data.

APPENDIX H
ORGAN WEIGHTS AND
ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE H1	Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 13-Week Drinking Water Study of Pyridine	H-2
TABLE H2	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine	H-3
TABLE H3	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Drinking Water Study of Pyridine	H-4

TABLE H1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 13-Week Drinking Water Study of Pyridine^a

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Male						
n	10	10	10	10	10	10
Necropsy body wt	335 ± 9	334 ± 7	337 ± 6	334 ± 7	316 ± 5	287 ± 5**
Heart						
Absolute	1.145 ± 0.034	1.187 ± 0.049	1.140 ± 0.038	1.140 ± 0.029	1.129 ± 0.059	1.159 ± 0.037
Relative	3.42 ± 0.08	3.56 ± 0.13	3.38 ± 0.08	3.42 ± 0.08	3.57 ± 0.17	4.04 ± 0.12**
R. Kidney						
Absolute	1.352 ± 0.037	1.333 ± 0.039	1.345 ± 0.032	1.398 ± 0.040	1.381 ± 0.026	1.396 ± 0.037
Relative	4.04 ± 0.05	3.99 ± 0.06	3.99 ± 0.05	4.18 ± 0.08	4.38 ± 0.08**	4.87 ± 0.08**
Liver						
Absolute	14.384 ± 0.601	14.901 ± 0.579	15.415 ± 0.429	16.091 ± 0.541*	16.535 ± 0.295*	15.512 ± 0.500*
Relative	42.81 ± 0.99	44.52 ± 0.77	45.75 ± 0.76*	48.07 ± 0.81**	52.41 ± 0.99**	54.06 ± 1.27**
Lung						
Absolute	1.837 ± 0.061	1.782 ± 0.048	1.791 ± 0.050	1.844 ± 0.077	1.747 ± 0.051	1.558 ± 0.053**
Relative	5.49 ± 0.16	5.36 ± 0.17	5.33 ± 0.17	5.51 ± 0.18	5.55 ± 0.20	5.43 ± 0.16
R. Testis						
Absolute	1.502 ± 0.026	1.474 ± 0.020	1.486 ± 0.025	1.502 ± 0.019	1.516 ± 0.013	1.437 ± 0.019
Relative	4.51 ± 0.15	4.43 ± 0.10	4.42 ± 0.08	4.50 ± 0.05	4.81 ± 0.07*	5.02 ± 0.08**
Thymus						
Absolute	0.320 ± 0.022	0.363 ± 0.031	0.352 ± 0.020	0.350 ± 0.018	0.362 ± 0.026	0.294 ± 0.023
Relative	0.95 ± 0.06	1.08 ± 0.07	1.04 ± 0.05	1.05 ± 0.04	1.15 ± 0.08	1.03 ± 0.08
Female						
n	10	10	10	10	10	8
Necropsy body wt	198 ± 3	196 ± 4	195 ± 2	197 ± 4	185 ± 2**	180 ± 3**
Heart						
Absolute	0.807 ± 0.033	0.752 ± 0.027	0.797 ± 0.030	0.786 ± 0.033	0.806 ± 0.029	0.767 ± 0.054
Relative	4.07 ± 0.16	3.83 ± 0.11	4.10 ± 0.17	3.99 ± 0.15	4.37 ± 0.18	4.26 ± 0.30
R. Kidney						
Absolute	0.752 ± 0.017	0.731 ± 0.018	0.741 ± 0.008	0.795 ± 0.012	0.774 ± 0.019	0.739 ± 0.024
Relative	3.80 ± 0.09	3.74 ± 0.10	3.81 ± 0.06	4.04 ± 0.05	4.19 ± 0.11**	4.10 ± 0.10*
Liver						
Absolute	6.866 ± 0.135	7.305 ± 0.133	7.874 ± 0.212**	8.732 ± 0.244**	9.391 ± 0.152**	9.619 ± 0.293**
Relative	34.68 ± 0.53	37.32 ± 0.76	40.46 ± 1.23**	44.30 ± 0.82**	50.80 ± 0.75**	53.44 ± 1.79**
Lung						
Absolute	1.277 ± 0.049	1.230 ± 0.048	1.253 ± 0.070	1.289 ± 0.059	1.290 ± 0.034	1.173 ± 0.022
Relative	6.46 ± 0.27	6.26 ± 0.15	6.45 ± 0.40	6.53 ± 0.22	6.98 ± 0.16	6.51 ± 0.07
Thymus						
Absolute	0.265 ± 0.011	0.295 ± 0.013	0.280 ± 0.008	0.305 ± 0.037	0.313 ± 0.034	0.252 ± 0.011
Relative	1.34 ± 0.06	1.50 ± 0.06	1.44 ± 0.04	1.54 ± 0.18	1.70 ± 0.19	1.39 ± 0.05

* Significantly different ($P \leq 0.05$) from the control group by Williams or Dunnett's test

** $P \leq 0.01$

^a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE H2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine^a

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
n	10	10	10	10	9	10
Necropsy body wt	490 ± 10	457 ± 12	469 ± 6	445 ± 17*	428 ± 8**	405 ± 15**
Heart						
Absolute	1.679 ± 0.043	1.730 ± 0.088	1.780 ± 0.051	1.712 ± 0.090	1.560 ± 0.081	1.513 ± 0.071
Relative	3.44 ± 0.09	3.78 ± 0.14	3.80 ± 0.13	3.84 ± 0.10	3.63 ± 0.13	3.74 ± 0.12
R. Kidney						
Absolute	1.948 ± 0.069	1.924 ± 0.061	2.004 ± 0.046	2.085 ± 0.079	2.041 ± 0.115	1.998 ± 0.114
Relative	3.98 ± 0.11	4.21 ± 0.09	4.27 ± 0.10	4.70 ± 0.13**	4.76 ± 0.21**	4.92 ± 0.19**
Liver						
Absolute	20.949 ± 0.624	21.152 ± 0.840	21.528 ± 0.608	21.706 ± 0.945	22.662 ± 1.098	21.367 ± 1.160
Relative	42.79 ± 0.98	46.33 ± 1.47	45.90 ± 1.25	48.78 ± 0.97**	52.77 ± 1.68**	52.60 ± 1.65**
Lung						
Absolute	2.534 ± 0.090	2.366 ± 0.129	2.429 ± 0.098	2.217 ± 0.104	2.133 ± 0.134	2.213 ± 0.111
Relative	5.22 ± 0.28	5.16 ± 0.20	5.20 ± 0.25	5.00 ± 0.19	4.97 ± 0.25	5.46 ± 0.19
R. Testis						
Absolute	1.737 ± 0.046	1.632 ± 0.074	1.843 ± 0.039	1.731 ± 0.051	1.939 ± 0.181	1.823 ± 0.085
Relative	3.56 ± 0.14	3.59 ± 0.17	3.93 ± 0.09	3.92 ± 0.12	4.50 ± 0.34**	4.52 ± 0.18**
Thymus						
Absolute	0.479 ± 0.039	0.501 ± 0.035	0.458 ± 0.026	0.499 ± 0.036	0.423 ± 0.029	0.507 ± 0.061
Relative	0.98 ± 0.08	1.11 ± 0.09	0.98 ± 0.06	1.12 ± 0.07	0.99 ± 0.06	1.23 ± 0.12

* Significantly different ($P \leq 0.05$) from the control group by Williams or Dunnett's test

** $P \leq 0.01$

^a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE H3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Drinking Water Study of Pyridine^a

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Male						
n	10	10	10	10	10	10
Necropsy body wt	38.9 ± 0.8	37.6 ± 1.1	38.8 ± 0.9	39.6 ± 1.2	38.8 ± 0.8	36.9 ± 0.7
Heart						
Absolute	0.199 ± 0.008	0.193 ± 0.010	0.211 ± 0.013	0.203 ± 0.010	0.188 ± 0.006	0.193 ± 0.008
Relative	5.12 ± 0.17	5.15 ± 0.26	5.41 ± 0.28	5.11 ± 0.19	4.85 ± 0.14	5.25 ± 0.19
R. Kidney						
Absolute	0.304 ± 0.007	0.291 ± 0.010	0.302 ± 0.016	0.293 ± 0.011	0.254 ± 0.009*	0.274 ± 0.008*
Relative	7.85 ± 0.24	7.76 ± 0.16	7.80 ± 0.43	7.41 ± 0.23	6.57 ± 0.26**	7.44 ± 0.24
Liver						
Absolute	1.855 ± 0.044	1.878 ± 0.048	2.058 ± 0.057*	2.177 ± 0.083**	2.264 ± 0.066**	2.249 ± 0.067**
Relative	47.81 ± 1.21	50.16 ± 1.06	53.08 ± 1.19**	54.85 ± 0.76**	58.36 ± 1.23**	60.96 ± 1.01**
Lung						
Absolute	0.281 ± 0.020	0.267 ± 0.017	0.293 ± 0.022	0.274 ± 0.018 ^b	0.288 ± 0.017	0.269 ± 0.008
Relative	7.31 ± 0.66	7.13 ± 0.44	7.54 ± 0.48	6.85 ± 0.41 ^b	7.46 ± 0.47	7.36 ± 0.33
R. Testis						
Absolute	0.125 ± 0.003	0.125 ± 0.004	0.127 ± 0.004	0.129 ± 0.004	0.123 ± 0.002	0.117 ± 0.004
Relative	3.22 ± 0.10	3.34 ± 0.07	3.27 ± 0.12	3.27 ± 0.10	3.18 ± 0.06	3.18 ± 0.12
Thymus						
Absolute	0.057 ± 0.007	0.059 ± 0.005	0.065 ± 0.007	0.057 ± 0.009	0.055 ± 0.005	0.047 ± 0.006
Relative	1.46 ± 0.17	1.59 ± 0.16	1.65 ± 0.17	1.42 ± 0.18	1.42 ± 0.13	1.28 ± 0.14
Female						
n	10	10	10	9	10	10
Necropsy body wt	33.0 ± 1.1	37.1 ± 1.1	33.9 ± 0.9	34.0 ± 1.1	32.9 ± 0.9	29.4 ± 0.9*
Heart						
Absolute	0.146 ± 0.007	0.157 ± 0.006	0.139 ± 0.003	0.134 ± 0.006	0.141 ± 0.006	0.129 ± 0.003*
Relative	4.45 ± 0.24	4.27 ± 0.21	4.13 ± 0.17	3.93 ± 0.10	4.28 ± 0.14	4.40 ± 0.12
R. Kidney						
Absolute	0.199 ± 0.006	0.219 ± 0.004	0.193 ± 0.010	0.203 ± 0.007	0.206 ± 0.004	0.204 ± 0.005
Relative	6.07 ± 0.14	5.94 ± 0.14	5.73 ± 0.32	5.97 ± 0.12	6.28 ± 0.14	6.98 ± 0.19**
Liver						
Absolute	1.513 ± 0.039	1.766 ± 0.039*	1.630 ± 0.044	1.743 ± 0.081*	1.836 ± 0.059**	1.609 ± 0.071
Relative	46.04 ± 1.09	47.80 ± 0.84	48.29 ± 1.67	51.04 ± 1.20**	55.71 ± 0.81**	54.69 ± 1.58**
Lung						
Absolute	0.263 ± 0.016	0.268 ± 0.015	0.224 ± 0.008	0.233 ± 0.009	0.252 ± 0.012	0.231 ± 0.012
Relative	7.98 ± 0.44	7.25 ± 0.41	6.60 ± 0.24*	6.90 ± 0.35	7.66 ± 0.32	7.91 ± 0.46
Thymus						
Absolute	0.062 ± 0.005	0.068 ± 0.004	0.060 ± 0.005	0.065 ± 0.005	0.056 ± 0.003	0.055 ± 0.003
Relative	1.87 ± 0.12	1.85 ± 0.12	1.78 ± 0.13	1.91 ± 0.15	1.72 ± 0.12	1.89 ± 0.10

* Significantly different (P≤0.05) from the control group by Williams or Dunnett's test

** P≤0.01

^a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

^b n=9

APPENDIX I

REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE I1	Summary of Reproductive Tissue Evaluations for Male F344/N Rats in the 13-Week Drinking Water Study of Pyridine	I-2
TABLE I2	Summary of Estrous Cycle Characterization for Female F344/N Rats in the 13-Week Drinking Water Study of Pyridine	I-2
TABLE I3	Summary of Reproductive Tissue Evaluations for Male Mice in the 13-Week Drinking Water Study of Pyridine	I-3
TABLE I4	Summary of Estrous Cycle Characterization for Female Mice in the 13-Week Drinking Water Study of Pyridine	I-3

TABLE II
Summary of Reproductive Tissue Evaluations for Male F344/N Rats in the 13-Week Drinking Water Study of Pyridine^a

	0 ppm	250 ppm	500 ppm	1,000 ppm
n	10	10	10	10
Weights (g)				
Necropsy body wt	339 ± 9	334 ± 7	316 ± 5*	287 ± 5**
L. cauda epididymis	0.1834 ± 0.0057	0.1866 ± 0.0040	0.1939 ± 0.0039	0.1785 ± 0.0042
L. epididymis	0.4590 ± 0.0105	0.4529 ± 0.0037	0.4723 ± 0.0030	0.4201 ± 0.0068**
L. testis	1.5272 ± 0.0165	1.5036 ± 0.0181	1.5726 ± 0.0150	1.4368 ± 0.0125**
Spermatid measurements				
Spermatid heads (10 ⁷ /g testis)	11.29 ± 0.72 ^b	10.86 ± 0.41 ^b	10.87 ± 0.35	11.36 ± 0.37
Spermatid heads (10 ⁷ /testis)	17.29 ± 1.17 ^b	16.31 ± 0.60 ^b	17.07 ± 0.49	16.33 ± 0.58
Spermatid count (mean/10 ⁻⁴ mL suspension)	86.47 ± 5.84 ^b	81.53 ± 3.01 ^b	85.33 ± 2.44	81.63 ± 2.88
Epididymal spermatozoal measurements				
Motility (%)	98.89 ± 0.19	98.96 ± 0.16	99.00 ± 0.13	98.87 ± 0.15
Concentration (10 ⁶ /g cauda epididymal tissue)	748 ± 34	733 ± 24	683 ± 18	714 ± 36

* Significantly different (P≤0.05) from the control group by Williams' test

** Significantly different (P≤0.01) from the control group by Williams' test (body weights) or Dunnett's test (epididymal and testis weights)

^a Data are presented as mean ± standard error. Differences from the control group are not significant by Dunnett's test (caudal weight) or Dunn's test (spermatid and epididymal spermatozoal measurements).

^b n=9

TABLE I2
Summary of Estrous Cycle Characterization for Female F344/N Rats in the 13-Week Drinking Water Study of Pyridine^a

	0 ppm	250 ppm	500 ppm	1,000 ppm
n	10	10	10	8
Necropsy body wt (g)	198 ± 3	197 ± 4	185 ± 2**	180 ± 3**
Estrous cycle length (days)	5.00 ± 0.00 ^b	5.00 ± 0.00	5.30 ± 0.30	6.08 ± 0.30** ^c
Estrous stages (% of cycle)				
Diestrus	42.5	45.8	40.8	54.2
Proestrus	13.3	16.7	16.7	12.5
Estrus	25.0	19.2	23.3	19.8
Metestrus	19.2	18.3	19.2	13.5

** Significantly different (P≤0.01) from the control group by Williams' test (body weights) or Shirley's test (estrous cycle length)

^a Necropsy body weight and estrous cycle length data are presented as mean ± standard error. By multivariate analysis of variance, exposed females do not differ significantly from the control females in the relative length of time spent in the estrous stages.

^b Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.

^c Estrous cycle was longer than 12 days or unclear in 2 of 8 animals.

TABLE I3
Summary of Reproductive Tissue Evaluations for Male Mice in the 13-Week Drinking Water Study of Pyridine^a

	0 ppm	250 ppm	500 ppm	1,000 ppm
n	10	10	10	10
Weights (g)				
Necropsy body wt	38.9 ± 0.8	39.6 ± 1.2	38.8 ± 0.8	36.9 ± 0.7
L. cauda epididymis	0.0170 ± 0.0011	0.0166 ± 0.0006	0.0170 ± 0.0008	0.0155 ± 0.0008
L. epididymis	0.0453 ± 0.0018	0.0480 ± 0.0016	0.0449 ± 0.0017	0.0446 ± 0.0019
L. testis	0.1174 ± 0.0036	0.1181 ± 0.0034	0.1169 ± 0.0033	0.1088 ± 0.0044
Spermatid measurements				
Spermatid heads (10 ⁷ /g testis)	15.81 ± 0.62	13.37 ± 0.56	15.53 ± 1.05	14.73 ± 1.10
Spermatid heads (10 ⁷ /testis)	1.85 ± 0.09	1.57 ± 0.05*	1.80 ± 0.11	1.61 ± 0.14
Spermatid count (mean/10 ⁻⁴ mL suspension)	57.90 ± 2.69	49.00 ± 1.69*	56.28 ± 3.37	50.45 ± 4.26
Epididymal spermatozoal measurements				
Motility (%)	99.31 ± 0.13	98.58 ± 0.12**	98.16 ± 0.26**	97.21 ± 0.42**
Concentration (10 ⁶ /g cauda epididymal tissue)	1,630 ± 126	1,432 ± 57	1,360 ± 54	1,461 ± 72

* Significantly different ($P \leq 0.05$) from the control group by Dunn's test

** Significantly different ($P \leq 0.01$) from the control group by Shirley's test

^a Data are presented as mean ± standard error. Differences from the control group are not significant by Dunnett's test (body and tissue weights) or Dunn's test (spermatid heads per gram testis and epididymal spermatozoal concentration).

TABLE I4
Summary of Estrous Cycle Characterization for Female Mice in the 13-Week Drinking Water Study of Pyridine^a

	0 ppm	250 ppm	500 ppm	1,000 ppm
n	10	9	10	10
Necropsy body wt (g)	33.0 ± 1.1	34.0 ± 1.1	32.9 ± 0.9	29.4 ± 0.9*
Estrous cycle length (days)	4.72 ± 0.55 ^b	4.50 ± 0.16 ^c	4.72 ± 0.22 ^b	4.28 ± 0.15 ^b
Estrous stages (% of cycle)				
Diestrus	36.7	35.2	31.7	31.7
Proestrus	20.0	13.9	17.5	20.0
Estrus	25.0	35.2	35.8	27.5
Metestrus	18.3	15.7	15.0	20.8

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test

^a Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the control group for estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, exposed females do not differ significantly from the control females in the relative length of time spent in the estrous stages.

^b Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.

^c Estrous cycle was longer than 12 days or unclear in 1 of 9 animals.

APPENDIX J

DETERMINATIONS

OF PYRIDINE IN PLASMA

TABLE J1	Plasma Concentrations of Pyridine in F344/N Rats in the 13-Week Drinking Water Study of Pyridine	J-2
TABLE J2	Plasma Concentrations of Pyridine in Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine	J-2

TABLE J1
Plasma Concentrations of Pyridine in F344/N Rats in the 13-Week Drinking Water Study of Pyridine^a

	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Male					
n	10	10	9	9	10
Concentration ($\mu\text{g/mL}$)	0.045 \pm 0.016	0.018 \pm 0.007	0.084 \pm 0.022	4.760 \pm 1.334	38.140 \pm 4.173
Female					
n	10	10	10	10	8
Concentration ($\mu\text{g/mL}$)	0.057 \pm 0.014	0.075 \pm 0.019	2.851 \pm 0.602	14.810 \pm 1.682	28.351 \pm 5.070

^a Mean \pm standard error

TABLE J2
Plasma Concentrations of Pyridine in Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine^a

	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
n	10	9	9	9	9
Concentration ($\mu\text{g/mL}$)	0.153 \pm 0.096	0.043 \pm 0.010	2.811 \pm 1.406	8.278 \pm 1.716	22.602 \pm 5.798

^a Mean \pm standard error

APPENDIX K

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF PYRIDINE	K-2
PREPARATION AND ANALYSIS OF DOSE FORMULATIONS	K-3
FIGURE K1 Infrared Absorption Spectrum of Pyridine	K-4
FIGURE K2 Nuclear Magnetic Resonance Spectrum of Pyridine	K-5
TABLE K1 Preparation and Storage of Dose Formulations in the Drinking Water Studies of Pyridine	K-6
TABLE K2 Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 13-Week Drinking Water Studies of Pyridine	K-7
TABLE K3 Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 2-Year Drinking Water Studies of Pyridine	K-10
TABLE K4 Results of Referee Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 13-Week Drinking Water Studies of Pyridine	K-17

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF PYRIDINE

Pyridine was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (00103BV), which was used during the 13-week and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the pyridine studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear colorless liquid, was identified as pyridine by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra (*Sadtler Standard Spectra*) of pyridine. The infrared and nuclear magnetic spectra are presented in Figures K1 and K2.

The purity of lot 00103BV was determined by elemental analyses, Karl Fischer water analysis, functional group titration, and gas chromatography. For amine group titration, the sample was dissolved in glacial acetic acid, then titrated with 0.1 N perchloric acid in glacial acetic acid to a potentiometric endpoint. The titration was monitored with a combination mV/pH electrode filled with aqueous 3 M potassium chloride. Gas chromatography was performed using a flame ionization detector. Two systems were used:

- A) 10% Carbowax 20M-TPA on 80/100 Chromosorb W AW glass column, with an isothermal oven temperature of 93° C, an oven temperature program of 60° C for 6 minutes, then 60° to 220° C at 10° C per minute, and a nitrogen carrier gas at a flow rate of 70 mL/minute, and
- B) DB-5 Capillary fused silica column, with an oven temperature program of 50° C for 5 minutes, then 50° to 250° C at 10° C per minute, and a helium carrier gas at a flow rate of 5 mL/minute.

Elemental analyses for hydrogen and nitrogen were in agreement with the theoretical values for pyridine; results for carbon were slightly low. Karl Fischer water analysis indicated 0.049% \pm 0.003% water. Functional group titration indicated a purity of 99.8% \pm 0.6%. Gas chromatography using systems A and B indicated one major peak and no impurities with an area greater than or equal to 0.1% relative to the major peak area. Concomitant analyses of lot 00103BV with lot 18400080202, a previously analyzed lot which was not used in the current studies, were performed with gas chromatography by system A but with an isothermal oven temperature of 95° C and with *n*-butanol as an internal standard. Results indicated a purity of 99.9% \pm 0.7% for lot 00103BV relative to lot 18400080202. The overall purity of lot 00103BV was determined to be greater than 99%.

The analytical chemistry laboratory conducted bulk stability studies on lot 18400080202 with gas chromatography. A flame ionization detector was used with a 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport glass column, a nitrogen carrier gas at a flow rate of 70 mL/minute, an oven temperature of 50° C, and a 0.4% ethyl acetate internal standard. Samples stored for 2 weeks at 25° or 60° C showed some decomposition. To ensure stability, the bulk chemical was stored at 1° to 7° C (13-week studies) or 2° to 8° C (2-year studies) in amber glass bottles in the dark. Stability was monitored during the studies using gas chromatography. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared as needed by mixing pyridine with deionized water (Table K1). Formulations were stored in Teflon®-capped amber glass bottles (13-week studies) or glass carboys (2-year studies) at room temperature in the dark for up to 3 weeks.

Stability studies of a 0.01 mg/mL formulation were performed by the analytical chemistry laboratory using high-performance liquid chromatography with a Waters μ Bondapak C18 column, ultraviolet (254 nm) detection, a solvent system of 0.005 M triethanolamine in water:methanol (30:70) with the pH adjusted to 7.0 with 10% phosphoric acid, and a flow rate of 1 mL/minute. The stability of the dose formulation was confirmed for at least 3 weeks when stored in the dark at room temperature. Solutions stored at room temperature exposed to air and light were also stable for 96 hours. In an earlier study by the analytical chemistry laboratory, the stability of a 19.64 mg/mL formulation was tested by gas chromatography using flame ionization detection, a 10% Carbowax 20 M/2% KOH on 80/100 mesh Chromosorb W AW silanized glass column, a nitrogen carrier gas at 25 mL/minute, and an oven temperature of 80° C. Stability was confirmed for 7 days at room temperature.

Periodic analyses of the dose formulations of pyridine were conducted at the study laboratory and the analytical chemistry laboratory using HPLC. For the 13-week studies, dose formulations were analyzed after preparation at the beginning, midpoint, and end of the studies (Table K2). During the 2-year studies, dose formulations were analyzed approximately every 6 to 10 weeks (Table K3). All dose formulations (45/45) analyzed and used during the 13-week studies were within 10% of the target concentration; 98% (44/45) of the animal room samples were within 10% of the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory during the 13-week studies agreed with the results obtained by the study laboratory (Table K4). Of the dose formulations analyzed during the 2-year studies, 99% (191/192) were within 10% of the target concentration. One formulation was 47% less than the target concentration; because records indicated that the proper amounts of pyridine and deionized water were used, it is possible that the wrong dose formulation was sampled for analysis. This dose formulation was remixed, and the remix was found to be within 10% of the target concentration. All animal room samples (75/75) were within 10% of the target concentration.

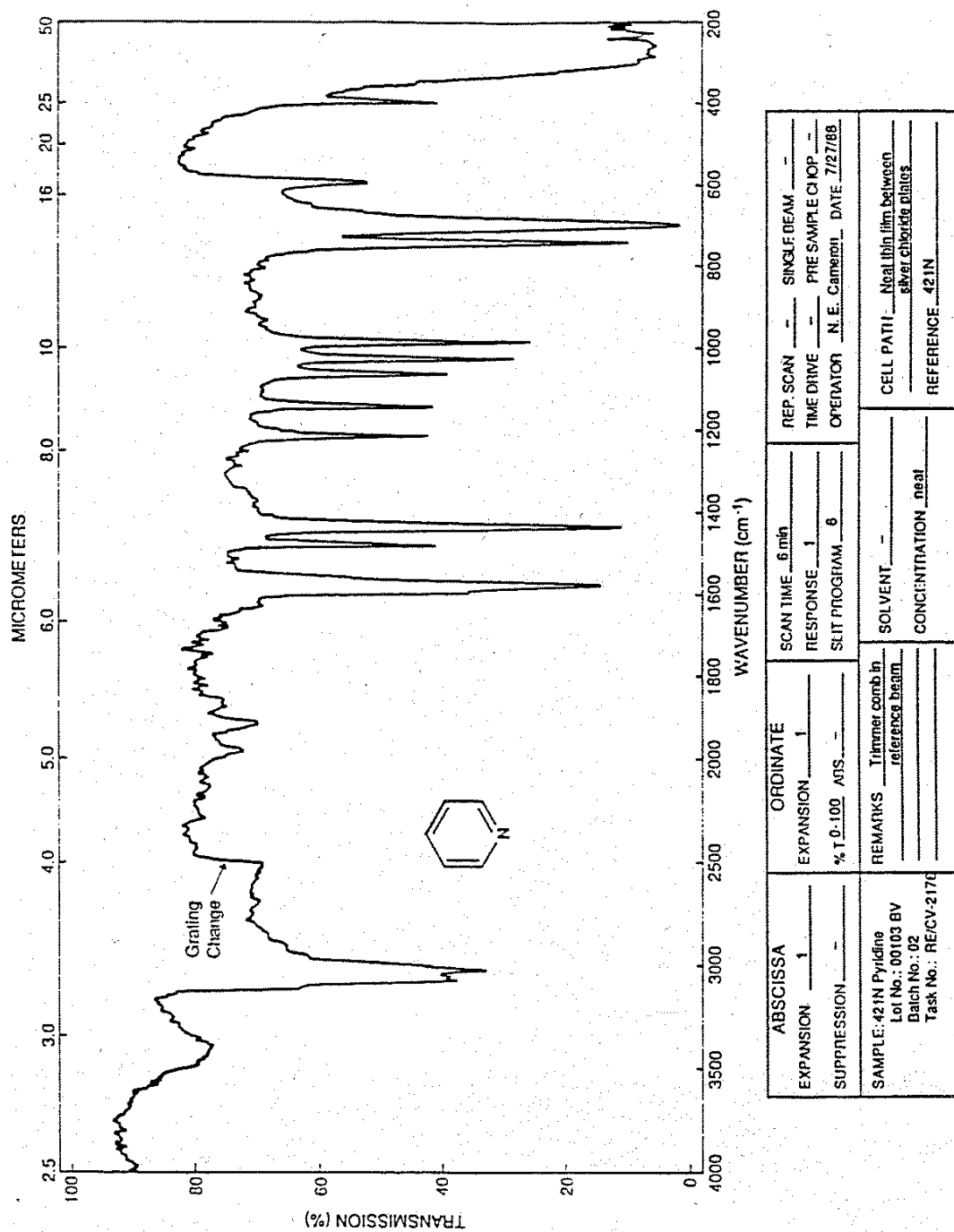


FIGURE K1
Infrared Absorption Spectrum of Pyridine

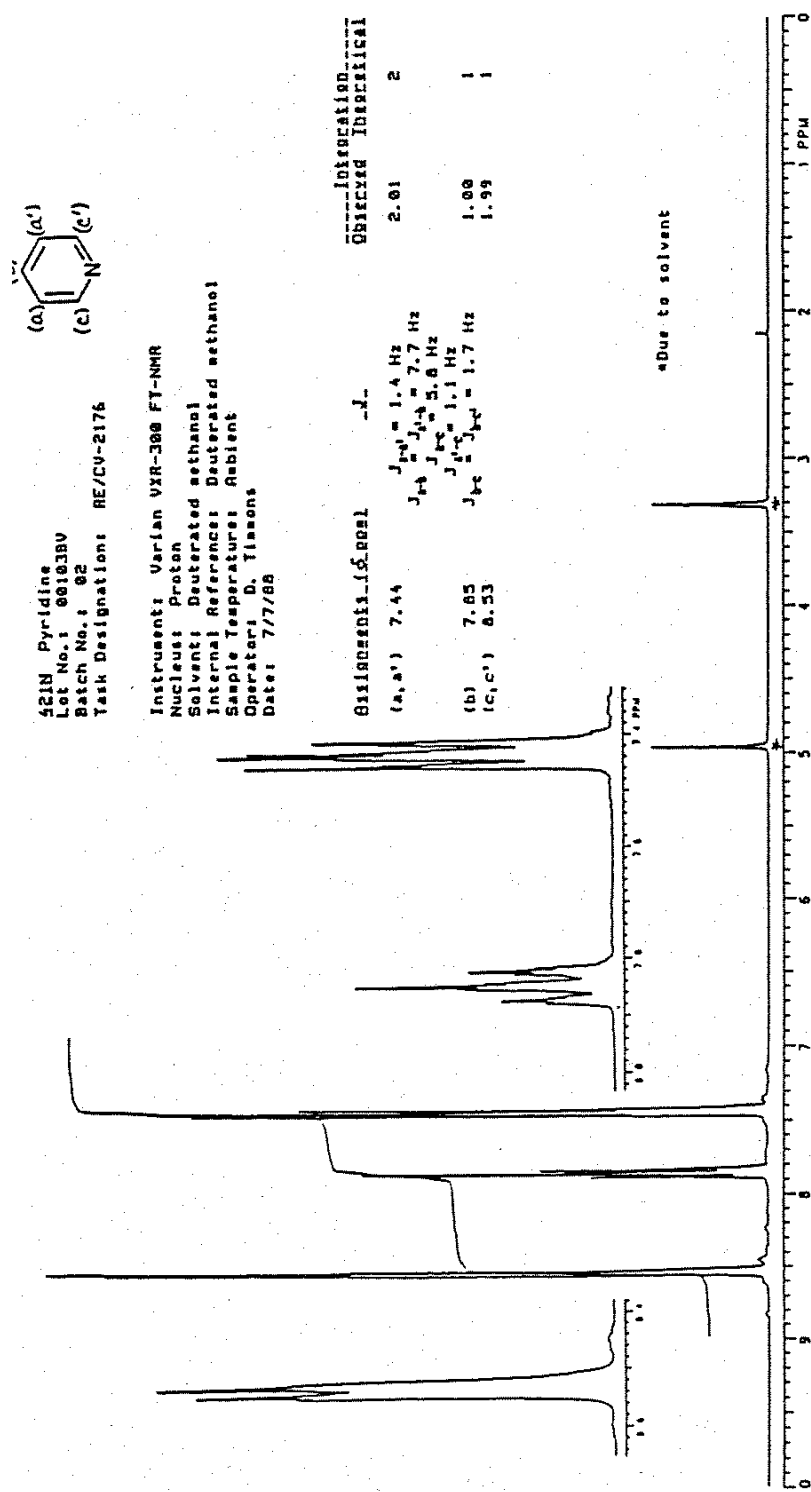


FIGURE K2
Nuclear Magnetic Resonance Spectrum of Pyridine

TABLE K1
Preparation and Storage of Dose Formulations in the Drinking Water Studies of Pyridine

13-Week Studies	2-Year Studies
Preparation Dose formulations were prepared as needed by combining weighed amounts of pyridine at room temperature and deionized water, then diluting to volume with additional water and mixing.	Same as 13-week studies
Chemical Lot Number 00103BV	00103BV
Maximum Storage Time 3 weeks	3 weeks
Storage Conditions Stored in sealed Teflon®-capped, amber glass bottles at room temperature in the dark	Stored in sealed glass carboys at room temperature in the dark
Study Laboratory TSI Mason Research Institute (Worcester, MA)	TSI Mason Laboratories (Worcester, MA)
Referee Laboratory Midwest Research Institute (Kansas City, MO)	None performed

TABLE K2
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 13-Week Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration ^a (mg/mL)	Determined Concentration ^b (mg/mL)	Difference from Target (%)
F344/N Rats				
11 January 1990	11 January 1990	0.05	0.048	-4
		0.10	0.097	-3
		0.25	0.235	-6
		0.50	0.492	-2
		1.00	0.989	-1
	26 January 1990 ^c	0.05	0.044	-12
		0.10	0.096	-4
		0.25	0.246	-2
		0.50	0.487	-3
		1.00	0.973	-3
1 March 1990	1 March 1990	0.05	0.051	+2
		0.10	0.100	0
		0.25	0.249	0
		0.50	0.501	0
		1.00	0.973	-3
	13 March 1990 ^c	0.05	0.053	+6
		0.10	0.100	0
		0.25	0.241	-4
		0.50	0.504	+1
		1.00	0.966	-3
12 April 1990	16 April 1990	0.05	0.050	0
		0.10	0.098	-2
		0.25	0.249	0
		0.50	0.502	0
		1.00	0.996	0
	25 April 1990 ^c	0.05	0.050	0
		0.10	0.097	-3
		0.25	0.249	0
		0.50	0.506	+1
		1.00	0.993	-1
Wistar Rats				
15 February 1990	16 February 1990	0.05	0.050	0
		0.10	0.100	0
		0.25	0.254	+2
		0.50	0.507	+1
		1.00	1.005	+1
	2 March 1990 ^c	0.05	0.050	0
		0.10	0.099	-1
		0.25	0.249	0
		0.50	0.493	-1
		1.00	0.998	0

TABLE K2
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 13-Week Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)	
Wistar Rats (continued)					
5 April 1990	5 April 1990	0.05	0.051	+2	
		0.10	0.101	+1	
		0.25	0.250	0	
		0.50	0.500	0	
		1.00	0.999	0	
	16 April 1990 ^c	0.05	0.049	-2	
		0.10	0.097	-3	
		0.25	0.248	-1	
		0.50	0.494	-1	
		1.00	0.996	0	
	17 May 1990	17 May 1990	0.05	0.048	-4
			0.10	0.099	-1
			0.25	0.248	-1
			0.50	0.494	-1
			1.00	1.006	+1
25 May 1990 ^c		0.05	0.050	0	
		0.10	0.098	-2	
		0.25	0.246	-2	
		0.50	0.495	-1	
		1.00	0.997	0	
Mice					
7 December 1989		7 December 1989	0.05	0.049	-2
			0.10	0.097	-3
			0.25	0.242	-3
			0.50	0.483	-3
	1.00		0.996	-3	
	27 December 1989 ^c	0.05	0.051	+2	
		0.10	0.099	-1	
		0.25	0.246	-2	
		0.50	0.504	+1	
		1.00	0.986	-1	
	25 January 1990	26 January 1990	0.05	0.052	+4
			0.10	0.097	-3
			0.25	0.246	-2
			0.50	0.487	-3
			1.00	0.981	-2
13 February 1990 ^c		0.05	0.049	-2	
		0.10	0.097	-3	
		0.25	0.240	-4	
		0.50	0.489	-2	
		1.00	0.973	-3	

TABLE K2

Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 13-Week Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)				
1 March 1990	1 March 1990	0.05	0.051	+2
		0.10	0.100	0
		0.25	0.249	0
		0.50	0.501	0
		1.00	0.973	-3
	13 March 1990 ^c	0.05	0.052	+4
		0.10	0.096	-4
		0.25	0.239	-4
		0.50	0.494	-1
		1.00	0.952	-5

^a 0.05 mg/mL=50 ppm; 0.10 mg/mL=100 ppm; 0.25 mg/mL=250 ppm; 0.50 mg/mL=500 ppm; 1.00 mg/mL=1,000 ppm

^b Results of duplicate analyses

^c Animal room samples

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 2-Year Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration ^a (mg/mL)	Determined Concentration ^b (mg/mL)	Difference from Target (%)
F344/N Rats				
11 April 1991	12 April 1991	0.1	0.100	0
		0.2	0.196	-2
		0.4	0.396	-1
	2 May 1991 ^c	0.1	0.099	-1
		0.2	0.199	0
		0.4	0.398	0
23 May 1991	24 May 1991	0.1	0.099	-1
		0.1	0.099	-1
		0.2	0.198	-1
		0.2	0.198	-1
		0.4	0.394	-1
		0.4	0.399	0
1 July 1991	1-3 July 1991	0.1	0.100	0
		0.1	0.100	0
		0.2	0.202	+1
		0.2	0.201	+1
		0.4	0.388	-3
		0.4	0.211	-47
3 July 1991	3 July 1991	0.4	0.398 ^d	0
29 August 1991	30 August 1991	0.1	0.101	+1
		0.1	0.098	-2
		0.2	0.197	-1
		0.2	0.191	-4
		0.4	0.347	-6
		0.4	0.390	-2
	20 September 1991 ^c	0.1	0.101	+1
		0.1	0.098	-2
		0.2	0.201	+1
		0.2	0.201	+1
24 October 1991	25 October 1991	0.1	0.102	+2
		0.2	0.209	+5
		0.4	0.416	+4
19 December 1991	20 December 1991	0.1	0.099	-1
		0.2	0.197	-1
		0.4	0.398	0

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 2-Year Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
F344/N Rats (continued)				
13 February 1992	14 February 1992	0.1	0.100	0
		0.2	0.198	-1
		0.4	0.392	-2
	3 March 1992 ^c	0.1	0.098	-2
		0.2	0.195	-2
		0.4	0.397	-1
	9 April 1992	0.1	0.100	0
		0.1	0.098	-2
		0.2	0.197	-1
		0.2	0.199	0
		0.4	0.392	-2
		0.4	0.402	+1
4 June 1992	5 June 1992	0.1	0.097	-3
		0.2	0.198	-1
		0.4	0.396	-1
30 July 1992	31 July 1992	0.1	0.098	-2
		0.2	0.193	-3
		0.4	0.393	-2
	2 September 1992 ^c	0.1	0.097	-3
		0.2	0.195	-2
		0.4	0.383	-4
	24 September 1992	0.1	0.102	+2
		0.2	0.201	+1
		0.4	0.399	0
19 November 1992	20-24 November 1992	0.1	0.101	+1
		0.2	0.206	+3
		0.4	0.395	-1
14 January 1993	15 January 1993	0.1	0.098	-2
		0.1	0.099	-1
		0.2	0.193	-3
		0.2	0.198	-1
		0.4	0.395	-1
		0.4	0.392	-2
	8 February 1993 ^c	0.1	0.090	-10
		0.1	0.095	-5
		0.2	0.195	-2
		0.2	0.195	-2
		0.4	0.386	-3
		0.4	0.386	-3
	11 March 1993	0.1	0.098	-2
		0.2	0.197	-1
		0.4	0.396	-1

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 2-Year Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Wistar Rats				
2 May 1991	2 May 1991	0.1	0.099	-1
		0.2	0.198	-1
		0.4	0.397	-1
	24 May 1991 ^c	0.1	0.099	-1
		0.2	0.197	-1
		0.4	0.398	0
1 July 1991	1-2 July 1991	0.1	0.100	0
		0.2	0.190	-5
		0.4	0.396	-1
29 August 1991	30 August 1991	0.1	0.099	-1
		0.2	0.197	-1
		0.4	0.408	+2
24 October 1991	25 October 1991	0.1	0.104	+4
		0.1	0.101	+1
		0.2	0.210	+5
		0.2	0.206	+3
		0.4	0.408	+2
		0.4	0.416	+4
	1 November 1991 ^c	0.1	0.095	-5
		0.1	0.098	-2
		0.2	0.197	-1
		0.2	0.197	-1
		0.4	0.403	+1
		0.4	0.403	+1
19 December 1991	20 December 1991	0.1	0.098	-2
		0.2	0.195	-2
		0.4	0.395	-1
13 February 1992	14 February 1992	0.1	0.100	0
		0.2	0.199	0
		0.4	0.398	0
9 April 1992	10 April 1992	0.1	0.100	0
		0.2	0.198	-1
		0.4	0.394	-1
	27 April 1992 ^c	0.1	0.099	-1
		0.2	0.198	-1
		0.4	0.421	+5
4 June 1992	5 June 1992	0.1	0.099	-1
		0.2	0.198	-1
		0.4	0.390	-2
30 July 1992	31 July 1992	0.1	0.099	-1
		0.2	0.195	-2
		0.4	0.390	-2

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 2-Year Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)	
Wistar Rats (continued)					
24 September 1992	25 September 1992	0.1	0.101	+1	
		0.2	0.200	0	
		0.4	0.385	-4	
	9 October 1992 ^c	0.1	0.100	0	
		0.2	0.198	-1	
		0.4	0.398	0	
	19 November 1992	20-24 November 1992	0.1	0.101	+1
			0.1	0.099	-1
			0.1	0.099	-1
0.2			0.202	+1	
0.2			0.198	-1	
0.2			0.199	0	
0.4			0.401	0	
0.4			0.399	0	
0.4			0.394	-1	
14 January 1993	15 January 1993	0.1	0.100	0	
		0.2	0.193	-3	
		0.4	0.389	-3	
11 March 1993	12 March 1993	0.1	0.100	0	
		0.2	0.197	-1	
		0.4	0.394	-1	
	1 April 1993 ^c	0.1	0.099	-1	
		0.2	0.197	-1	
		0.4	0.393	-2	
22 April 1993	23 April 1993	0.1	0.102	+2	
		0.2	0.201	+1	
		0.4	0.405	+1	
Male Mice					
21 March 1991	22 March 1991	0.25	0.249	0	
		0.50	0.498	0	
		1.00	0.990	-1	
	12 April 1991 ^c	0.25	0.246	-2	
		0.50	0.492	-2	
		1.00	0.979	-2	
9 May 1991	10 May 1991	0.25	0.244	-2	
		0.50	0.494	-1	
		1.00	0.981	-2	
1 July 1991	1 July 1991	0.25	0.246	-2	
		0.50	0.491	-2	
		1.00	0.986	-1	

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 2-Year Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Male Mice (continued)				
29 August 1991	30 August 1991	0.25	0.236	-6
		0.50	0.479	-4
		1.00	0.944	-6
	20 September 1991 ^c	0.25	0.251	0
		0.50	0.513	+3
		1.00	1.000	0
24 October 1991	25 October 1991	0.25	0.258	+3
		0.50	0.520	+4
		1.00	1.025	+3
19 December 1991	20 December 1991	0.25	0.255	+2
		0.50	0.500	0
		1.00	0.991	-1
13 February 1992	14 February 1992	0.25	0.246	-2
		0.50	0.489	-2
		1.00	0.990	-1
	3 March 1992 ^c	0.25	0.244	-2
		0.50	0.488	-2
		1.00	0.977	-2
9 April 1992	10 April 1992	0.25	0.245	-2
		0.50	0.484	-3
		1.00	0.981	-2
4 June 1992	5 June 1992	0.25	0.246	-2
		0.50	0.487	-3
		1.00	0.970	-3
30 July 1992	31 July 1992	0.25	0.245	-2
		0.50	0.492	-2
		1.00	0.973	-3
	2 September 1992 ^c	0.25	0.244	-2
		0.50	0.501	0
		1.00	0.988	-1
24 September 1992	25 September 1992	0.25	0.253	+1
		0.50	0.495	-1
		1.00	0.999	0
19 November 1992	20-24 November 1992	0.25	0.247	-1
		0.50	0.496	-1
		1.00	0.987	-1
14 January 1993	15 January 1993	0.25	0.250	0
		0.50	0.487	-3
		1.00	0.972	-3
	8 February 1993 ^c	0.25	0.245	-2
		0.50	0.476	-5
		1.00	0.961	-4

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 2-Year Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Male Mice (continued)				
11 March 1993	12 March 1993	0.25	0.252	+1
		0.50	0.497	-1
		1.00	0.981	-2
Female Mice				
21 March 1991	22 March 1991	0.125	0.124	-1
		0.250	0.248	-1
		0.500	0.504	+1
	12 April 1991 ^c	0.125	0.126	+1
		0.250	0.244	-2
		0.500	0.495	-1
9 May 1991	10 May 1991	0.125	0.122	-2
		0.250	0.246	-2
		0.500	0.490	-2
1 July 1991	1 July 1991	0.125	0.124	-1
		0.250	0.251	0
		0.500	0.494	-1
29 August 1991	30 August 1991	0.125	0.118	-6
		0.250	0.234	-6
		0.500	0.473	-5
	20 September 1991 ^c	0.125	0.125	0
		0.250	0.245	-2
		0.500	0.499	0
24 October 1991	25 October 1991	0.125	0.126	+1
		0.250	0.260	+4
		0.500	0.517	+3
19 December 1991	20 December 1991	0.125	0.127	+2
		0.250	0.248	-1
		0.500	0.495	-1
13 February 1992	14 February 1992	0.125	0.125	0
		0.250	0.247	-1
		0.500	0.491	-2
	3 March 1992 ^c	0.125	0.124	-1
		0.250	0.248	-1
		0.500	0.490	-2
9 April 1992	10 April 1992	0.125	0.123	-2
		0.250	0.245	-2
		0.500	0.491	-2
4 June 1992	5 June 1992	0.125	0.120	-4
		0.250	0.243	-3
		0.500	0.488	-2

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice
in the 2-Year Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Female Mice (continued)				
30 July 1992	31 July 1992	0.125	0.127	+2
		0.250	0.244	-2
		0.500	0.491	-2
	2 September 1992 ^c	0.125	0.126	+1
		0.250	0.249	0
		0.500	0.502	0
24 September 1992	25 September 1992	0.125	0.127	+2
		0.250	0.253	+1
		0.500	0.494	-1
19 November 1992	20-24 November 1992	0.125	0.125	0
		0.250	0.249	0
		0.500	0.482	-4
14 January 1993	15 January 1993	0.125	0.122	-2
		0.250	0.245	-2
		0.500	0.483	-3
	8 February 1993 ^c	0.125	0.118	-6
		0.250	0.245	-2
		0.500	0.483	-3
11 March 1993	12 March 1993	0.125	0.127	+2
		0.250	0.247	-1
		0.500	0.498	0

^a 0.1 mg/mL=100 ppm; 0.125 mg/mL=125 ppm; 0.2 mg/mL=200 ppm; 0.25 mg/mL=250 ppm; 0.4 mg/mL=400 ppm;

0.50 mg/mL=500 ppm; 1.00 mg/mL=1,000 ppm

^b Results of duplicate analyses

^c Animal room samples

^d Results of remix

TABLE K4

Results of Referee Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 13-Week Drinking Water Studies of Pyridine

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory ^a	Referee Laboratory ^b
F344/N Rats			
11 January 1990	0.50	0.492	0.512 ± 0.005
Wistar Rats			
15 February 1990	1.00	1.005	0.994 ± 0.002
Mice			
7 December 1989	0.10	0.097	0.106 ± 0.000

^a Results of duplicate analyses

^b Results of triplicate analyses (mean ± standard error)

APPENDIX L

WATER AND COMPOUND CONSUMPTION IN THE 2-YEAR DRINKING WATER STUDIES OF PYRIDINE

TABLE L1	Water and Compound Consumption by Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine	L-2
TABLE L2	Water and Compound Consumption by Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine	L-3
TABLE L3	Water and Compound Consumption by Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine	L-4
TABLE L4	Water and Compound Consumption by Male Mice in the 2-Year Drinking Water Study of Pyridine	L-5
TABLE L5	Water and Compound Consumption by Female Mice in the 2-Year Drinking Water Study of Pyridine	L-6

TABLE L1
Water and Compound Consumption by Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

Week	0 ppm		100 ppm			200 ppm			400 ppm		
	Water (g/day) ^a	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose/ Day ^b (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	20.4	136	19.5	135	14	18.6	135	28	18.5	136	55
2	21.4	173	20.7	172	12	20.9	169	25	21.5	167	51
3	22.6	207	22.1	208	11	21.8	206	21	24.3	201	48
4	20.5	236	21.2	234	9	19.9	232	17	24.1	227	43
5	22.1	255	21.6	253	9	23.0	250	18	23.4	245	38
6	20.6	275	21.1	267	8	21.7	272	16	22.6	258	35
7	20.4	293	20.7	286	7	21.5	289	15	22.8	272	34
8	22.4	302	22.8	295	8	22.6	295	15	24.9	282	35
9	22.4	314	22.4	309	7	22.5	306	15	24.7	291	34
10	23.3	331	22.9	326	7	21.8	323	14	25.8	309	33
11	22.3	333	21.4	329	7	22.0	328	13	26.9	311	35
12	24.9	342	23.6	339	7	22.7	340	13	26.9	323	33
13	21.5	351	20.6	349	6	21.6	348	12	24.6	328	30
17	21.8	384	21.4	382	6	20.3	378	11	23.8	355	27
21	22.5	409	21.3	405	5	22.1	404	11	23.6	376	25
25	22.4	426	22.2	420	5	22.7	420	11	25.7	392	26
29	22.7	437	23.0	431	5	22.7	433	11	25.7	403	26
33	22.9	453	23.3	448	5	23.5	448	11	24.8	421	24
37	24.5	465	21.8	461	5	22.3	460	10	25.0	434	23
41	25.3	478	22.8	468	5	25.0	469	11	25.7	443	23
45	21.6	483	20.8	480	4	20.8	480	9	23.1	452	20
49	22.4	489	20.9	479	4	22.3	480	9	24.1	453	21
53	21.7	487	21.6	482	5	22.3	482	9	25.8	453	23
57	23.8	502	23.0	489	5	26.1	484	11	29.3	462	25
61	24.1	503	22.7	491	5	25.4	487	10	28.7	459	25
65	26.0	508	25.4	492	5	28.8	484	12	32.3	455	28
69	25.0	511	24.3	500	5	29.0	485	12	35.2	457	31
73	25.6	511	25.7	500	5	30.0	480	13	37.4	446	34
77	24.5	510	24.1	497	5	27.9	475	12	35.8	446	32
81	26.1	494	26.5	497	5	30.1	467	13	40.3	441	37
85	27.7	501	28.3	486	6	35.5	462	15	45.1	428	42
89	29.3	499	29.8	484	6	34.7	440	16	43.7	414	42
93	32.5	501	31.7	478	7	38.0	428	18	46.7	406	46
97	30.6	491	29.2	464	6	35.0	414	17	40.3	391	41
101	36.3	468	36.6	458	8	37.0	397	19	49.0	388	51
Mean for weeks											
1-13	21.9	273	21.6	270	9	21.6	269	17	23.9	258	39
14-52	22.9	447	21.9	441	5	22.4	441	10	24.6	414	24
53-101	27.2	499	26.8	486	6	30.8	460	14	37.6	434	35

^a Grams of water consumed per animal per day

^b Milligrams of pyridine consumed per kilogram body weight per day

TABLE L2
Water and Compound Consumption by Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

Week	0 ppm		100 ppm			200 ppm			400 ppm		
	Water (g/day) ^a	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose/ Day ^b (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	16.2	110	16.9	110	15	16.7	110	30	17.4	111	63
2	16.4	129	16.7	128	13	17.1	127	27	18.7	124	60
3	16.4	144	16.9	145	12	18.0	143	25	17.7	139	51
4	15.2	152	16.1	152	11	16.8	151	17	16.9	148	46
5	17.2	160	15.2	160	10	15.1	159	17	17.1	155	44
6	16.7	167	14.5	167	9	14.5	164	18	16.5	160	41
7	15.3	173	15.5	173	9	15.3	171	18	16.6	167	40
8	16.2	180	16.7	179	9	16.0	176	18	17.2	170	41
9	16.3	183	17.5	183	10	17.0	178	19	18.8	173	43
10	16.2	186	16.9	185	9	17.0	181	19	18.5	175	42
11	16.0	192	16.5	190	9	17.6	185	19	17.1	178	38
12	15.3	196	15.9	194	8	16.1	187	17	16.2	182	36
13	14.3	198	14.7	197	8	15.0	191	16	15.7	185	34
17	14.3	213	16.1	210	8	17.0	204	17	17.3	196	35
21	14.8	223	15.4	220	7	16.6	212	16	17.4	205	34
25	15.9	228	16.1	225	7	16.3	218	15	18.2	208	35
29	15.1	234	16.3	233	7	17.3	224	15	18.7	214	35
33	17.0	242	17.2	238	7	17.7	228	16	19.3	220	35
37	14.9	251	15.6	247	6	16.4	239	14	16.8	225	30
41	16.9	261	17.2	257	7	17.7	247	14	20.0	234	34
45	14.6	270	15.6	269	6	16.7	257	13	17.6	240	29
49	15.5	279	16.2	280	6	15.3	266	12	17.9	247	29
53	15.8	285	16.4	287	6	17.3	273	13	18.6	252	30
57	17.2	288	18.1	290	6	17.7	273	13	21.0	255	33
61	16.5	299	17.1	297	6	18.7	280	13	20.7	258	32
65	18.7	301	19.1	302	6	18.8	284	13	22.6	259	35
69	18.7	310	18.7	308	6	20.4	289	14	23.1	269	34
73	19.0	314	18.8	313	6	20.9	292	14	24.2	275	35
77	19.3	322	19.7	313	6	19.6	299	13	23.3	282	33
81	19.5	326	21.3	323	7	21.6	299	15	23.6	283	33
85	21.0	330	23.0	327	7	24.0	306	16	26.5	281	38
89	18.0	331	20.0	328	6	19.9	306	13	22.5	286	32
93	21.2	338	24.6	332	7	24.3	307	16	27.7	286	39
95	19.5	334	20.8	335	6	21.4	305	14	23.9	281	34
97	20.3	344	21.9	332	7	24.0	306	16	23.9	286	34
99	19.6	340	20.7	333	6	21.5	301	14	21.2	286	30
101	18.9	337	21.6	333	7	24.0	298	16	23.3	284	33
104	20.6	342	21.2	327	7	24.4	303	16	26.2	289	36
Mean for weeks											
1-13	16.0	167	16.2	166	10	16.3	163	21	17.3	159	45
14-52	15.4	245	16.2	242	7	16.8	233	15	18.1	221	33
53-104	19.0	321	20.2	318	6	21.2	295	14	23.3	276	34

^a Grams of water consumed per animal per day

^b Milligrams of pyridine consumed per kilogram body weight per day

TABLE L3
Water and Compound Consumption by Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

Week	0 ppm		100 ppm			200 ppm			400 ppm		
	Water (g/day) ^a	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose/ Day ^b (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	37.6	201	37.5	198	19	39.3	199	40	35.9	198	72
2	40.9	255	38.9	250	16	39.8	246	32	37.9	240	63
3	38.9	294	40.2	289	14	41.3	285	29	41.9	280	60
4	42.1	327	42.1	326	13	43.9	321	27	42.7	312	55
5	46.3	357	48.6	359	14	48.5	347	28	45.7	345	53
6	39.4	382	39.3	380	10	39.9	372	21	38.9	358	43
7	40.8	413	44.3	411	11	44.4	402	22	46.0	388	47
8	47.4	426	43.5	428	10	47.1	412	23	45.6	400	46
9	53.3	448	49.2	446	11	49.5	435	23	48.7	419	47
10	42.7	464	41.4	463	9	43.3	452	19	43.2	431	40
11	50.3	479	46.3	478	10	47.0	463	20	47.0	443	42
12	48.2	494	47.3	492	10	47.3	479	20	43.9	457	38
13	46.8	506	46.7	503	9	46.6	490	19	46.3	466	40
17	44.0	546	42.3	542	8	41.9	527	16	41.0	502	33
21	46.5	569	42.8	575	7	41.5	562	15	44.8	528	34
25	41.9	599	39.4	602	7	41.0	583	14	42.9	552	31
29	40.4	627	36.7	630	6	40.0	612	13	41.6	576	29
33	43.6	658	42.8	657	7	39.9	638	13	44.2	599	30
37	46.8	672	46.6	673	7	48.1	651	15	48.6	610	32
41	38.4	691	38.8	686	6	39.2	664	12	40.3	627	26
45	43.5	715	42.9	711	6	43.0	684	13	44.0	642	27
49	40.5	736	40.5	719	6	41.9	695	12	44.5	654	27
53	50.9	755	48.3	735	7	52.6	705	15	53.5	662	32
57	45.4	774	47.3	748	6	48.8	714	14	50.7	668	30
61	54.7	789	53.9	753	7	59.4	718	17	57.4	669	34
65	49.8	795	52.5	757	7	55.6	720	15	55.7	661	34
69	54.3	800	55.5	739	8	56.7	699	16	58.2	658	35
73	54.6	803	60.1	736	8	59.8	706	17	62.6	657	38
77	56.3	797	60.5	725	8	63.2	717	18	63.7	644	40
81	58.1	799	66.8	698	10	64.3	698	18	62.2	624	40
85	60.1	782	65.1	707	9	64.4	699	18	57.4	630	36
89	60.5	775	68.4	692	10	67.0	676	20	64.6	614	42
93	69.3	779	69.2	678	10	67.7	657	21	57.7	612	38
97	66.1	757	71.2	675	11	61.2	618	20	55.7	590	38
101	59.6	725	59.0	675	9	54.5	578	19	57.5	604	38
Mean for weeks											
1-13	44.2	388	43.5	386	12	44.5	377	25	43.4	364	50
14-52	42.8	646	41.4	644	6	41.8	624	14	43.5	588	30
53-101	56.9	779	59.8	717	8	59.6	685	17	58.2	638	37

^a Grams of water consumed per animal per day

^b Milligrams of pyridine consumed per kilogram body weight per day

TABLE L4
Water and Compound Consumption by Male Mice in the 2-Year Drinking Water Study of Pyridine

Week	0 ppm		250 ppm			500 ppm			1,000 ppm		
	Water (g/day) ^a	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose/ Day ^b (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	6.5	26.1	6.8	25.9	66	5.7	25.8	109	5.6	25.8	218
2	5.7	27.6	5.6	27.4	51	5.2	27.3	95	4.5	26.6	171
3	5.6	29.2	5.3	28.7	46	5.2	29.0	90	4.3	28.4	150
4	5.7	30.9	5.3	30.5	44	5.0	30.7	82	4.3	30.1	142
5	5.6	32.8	5.3	32.3	41	5.5	32.2	85	4.9	30.6	160
6	5.3	33.9	5.0	34.2	36	4.6	33.5	69	3.9	32.0	123
7	5.5	35.4	5.0	35.4	35	4.9	35.3	69	3.8	33.9	112
8	5.0	37.6	4.9	37.1	33	4.6	36.7	63	3.9	35.6	110
9	5.4	38.7	5.2	37.9	34	5.0	37.7	66	4.3	36.5	119
10	5.4	39.6	5.7	40.1	36	5.2	39.8	65	4.4	37.7	117
11	5.7	40.6	6.4	41.0	39	5.3	41.0	64	4.5	38.8	117
12	5.5	41.8	5.8	42.3	34	5.0	41.7	60	5.0	39.8	126
13	5.5	42.4	5.9	42.9	34	5.6	42.7	66	5.2	40.6	129
17	5.2	47.0	5.3	46.2	28	5.2	45.9	57	4.3	43.5	99
21	6.9	48.1	6.5	48.3	34	5.8	47.4	61	4.1	45.2	90
25	5.3	50.0	5.4	49.6	27	5.1	49.9	51	4.7	47.5	98
29	7.0	49.6	6.6	50.8	32	7.1	51.3	69	5.6	48.5	116
33	5.2	51.6	5.1	51.7	25	4.9	51.1	48	4.5	50.0	91
37	5.4	53.2	5.2	52.9	24	4.7	53.0	45	4.3	51.8	84
41	6.8	54.5	6.9	53.8	32	6.4	53.7	60	6.6	52.5	126
45	5.8	54.1	6.4	53.9	30	6.0	54.4	55	5.0	52.7	95
49	6.6	55.3	6.0	54.6	28	7.2	55.4	65	4.9	53.4	92
53	6.1	55.4	5.8	55.6	26	5.7	56.2	51			
57	6.5	55.2	6.6	55.4	30	6.3	56.0	56	5.7	54.0	106
61	5.9	55.2	6.0	56.1	27	5.7	56.4	51	4.7	54.2	88
65	5.6	54.4	6.0	56.3	27	5.6	56.1	50	4.3	54.1	80
69	5.8	55.1	6.8	56.5	30	6.7	55.5	61	5.2	54.4	96
73	5.8	54.4	6.5	56.6	29	6.6	53.9	61	4.7	54.1	87
77	5.8	52.8	7.2	55.1	32	7.0	52.2	67	5.2	52.4	99
81	5.8	51.4	7.7	53.7	36	7.4	50.2	74	5.1	49.2	105
85	6.0	49.2	7.4	51.5	36	7.2	47.8	75	5.2	47.3	109
89	5.5	46.6	8.4	49.7	42	7.0	45.8	76	5.4	45.6	119
93	5.4	45.5	8.2	46.4	44	7.3	44.7	81	5.4	43.7	122
97	6.6	43.8	8.0	43.6	46	7.7	42.9	89	6.0	41.8	144
99	6.2	44.5	8.4	43.5	48	7.7	42.7	91	6.0	41.2	146
101	6.3	44.2	7.7	41.9	46	8.0	41.6	96	6.1	40.6	150
Mean for weeks											
1-13	5.6	35.1	5.6	35.1	41	5.1	34.9	75	4.5	33.6	138
14-52	6.0	51.5	5.9	51.3	29	5.8	51.3	57	4.9	49.5	99
53-101	6.0	50.6	7.2	51.6	36	6.9	50.1	70	5.3	48.7	112

^a Grams of water consumed per animal per day

^b Milligrams of pyridine consumed per kilogram body weight per day

TABLE L5
Water and Compound Consumption by Female Mice in the 2-Year Drinking Water Study of Pyridine

Week	0 ppm		125 ppm			250 ppm			500 ppm		
	Water (g/day) ^a	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose/ Day ^b (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	7.3	20.8	7.5	20.7	45	6.8	20.6	82	6.3	20.5	154
2	6.9	21.8	6.6	21.4	39	6.6	21.6	76	5.7	21.5	132
3	7.5	23.2	7.1	22.8	39	7.4	22.8	81	6.5	22.6	144
4	6.5	24.1	6.8	24.0	35	6.4	23.9	67	5.6	23.7	118
5	7.7	25.5	7.0	25.3	34	6.9	25.5	68	5.4	25.6	106
6	6.1	26.7	5.8	26.5	28	6.3	26.3	59	4.9	26.9	90
7	5.8	28.2	5.8	28.4	25	6.1	28.8	53	5.1	28.5	89
8	6.0	29.6	5.4	29.9	23	5.6	29.8	47	5.0	30.0	84
9	5.9	31.1	5.7	30.1	24	5.7	30.8	46	5.2	30.4	85
10	5.5	31.7	6.3	32.0	24	6.4	32.7	49	5.7	32.9	86
11	6.7	33.3	6.3	33.2	24	6.2	33.7	46	5.7	33.7	85
12	7.1	34.1	6.4	34.2	23	6.0	35.2	43	5.4	35.1	76
13	6.1	35.8	5.7	35.5	20	5.4	36.5	37	5.4	36.3	74
17	5.0	40.2	4.8	39.4	15	5.1	40.5	31	5.1	40.4	64
21	11.5	41.1	6.8	40.0	21	6.9	41.6	41	8.6	41.4	104
25	4.5	45.9	4.6	44.2	13	4.4	45.8	24	4.3	45.1	48
29	5.3	45.7	5.0	44.9	14	4.4	47.2	23	5.5	46.5	60
33	4.9	49.1	4.6	47.7	12	4.4	49.5	22	4.3	48.7	44
37	4.4	51.0	4.4	49.4	11	4.4	51.0	22	4.2	50.1	42
41	5.9	53.1	6.3	51.1	15	5.8	53.2	27	6.2	52.0	60
45	5.8	54.0	5.7	52.5	14	5.6	54.1	26	6.1	52.2	58
49	5.5	56.2	5.4	54.5	12	6.3	55.6	28	6.3	54.4	58
53	5.2	56.9	5.0	55.6	11	5.2	57.1	23	5.8	55.5	52
57	5.4	58.2	5.1	56.4	11	5.6	58.0	24	5.2	56.8	46
61	4.8	59.5	4.8	57.9	10	4.8	59.3	20	4.9	58.1	42
65	4.6	59.9	5.0	58.5	11	4.6	61.0	19	5.0	58.6	42
69	5.1	61.6	6.0	59.3	13	5.7	62.1	23	6.1	58.2	53
73	4.9	62.8	5.4	60.2	11	5.1	62.2	20	6.4	58.0	55
77	5.0	63.3	5.4	61.0	11	6.2	61.9	25	7.8	55.4	71
81	4.6	62.2	4.9	60.3	10	5.8	60.4	24	7.3	51.6	70
85	4.9	61.1	5.4	58.6	11	7.7	58.8	33	8.6	48.7	89
89	2.6	60.0	2.7	58.0	6	3.4	54.4	16	3.2	45.8	35
93	5.8	57.4	7.1	56.3	16	9.7	50.9	47	8.5	43.7	97
97	6.0	55.7	7.8	52.7	18	10.4	47.1	55	8.6	40.2	106
99	6.0	56.1	8.4	53.3	20	10.1	46.1	55	8.0	40.1	100
101	5.4	55.5	9.2	52.5	22	10.7	42.8	62	8.0	39.9	100
104	5.9	55.3	8.7	49.0	22	10.7	41.5	64	8.0	38.0	106
Mean for weeks											
1-13	6.5	28.1	6.3	28.0	30	6.3	28.3	58	5.5	28.3	102
14-52	5.8	48.5	5.3	47.1	14	5.3	48.7	27	5.6	47.9	60
53-104	5.1	59.0	6.1	56.6	14	7.0	54.9	34	6.8	49.9	71

^a Grams of water consumed per animal per day

^b Milligrams of pyridine consumed per kilogram body weight per day

APPENDIX M
INGREDIENTS, NUTRIENT COMPOSITION,
AND CONTAMINANT LEVELS
IN NIH-07 RAT AND MOUSE RATION

TABLE M1	Ingredients of NIH-07 Rat and Mouse Ration	M-2
TABLE M2	Vitamins and Minerals in NIH-07 Rat and Mouse Ration	M-2
TABLE M3	Nutrient Composition of NIH-07 Rat and Mouse Ration	M-3
TABLE M4	Contaminant Levels in NIH-07 Rat and Mouse Ration	M-4

TABLE M1
Ingredients of NIH-07 Rat and Mouse Ration^a

Ingredients ^b	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer s yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

^a NCI, 1976; NIH, 1978

^b Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE M2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration^a

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D ₃	4,600,000 IU	D-activated animal sterol
K ₃	2.8 g	Menadione
<i>d</i> - α -Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
<i>d</i> -Pantothenic acid	18.0 g	<i>d</i> -Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B ₁₂	4,000 μ g	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	<i>d</i> -Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

^a Per ton (2,000 lb) of finished product

TABLE M3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean \pm Standard Deviation	Range		Number of Samples
Protein (% by weight)	23.45 \pm 0.49	22.3	24.3	26
Crude fat (% by weight)	5.34 \pm 0.18	5.00	5.90	26
Crude fiber (% by weight)	3.32 \pm 0.32	2.60	4.30	26
Ash (% by weight)	6.42 \pm 0.21	5.94	6.81	26
Amino Acids (% of total diet)				
Arginine	1.273 \pm 0.083	1.100	1.390	12
Cystine	0.307 \pm 0.068	0.181	0.400	12
Glycine	1.152 \pm 0.051	1.060	1.220	12
Histidine	0.581 \pm 0.029	0.531	0.630	12
Isoleucine	0.913 \pm 0.034	0.867	0.965	12
Leucine	1.969 \pm 0.053	1.850	2.040	12
Lysine	1.269 \pm 0.050	1.200	1.370	12
Methionine	0.436 \pm 0.104	0.306	0.699	12
Phenylalanine	0.999 \pm 0.114	0.665	1.110	12
Threonine	0.899 \pm 0.059	0.824	0.985	12
Tryptophan	0.216 \pm 0.146	0.107	0.671	12
Tyrosine	0.690 \pm 0.091	0.564	0.794	12
Valine	1.079 \pm 0.057	0.962	1.170	12
Essential Fatty Acids (% of total diet)				
Linoleic	2.389 \pm 0.223	1.830	2.570	11
Linolenic	0.273 \pm 0.034	0.210	0.320	11
Vitamins				
Vitamin A (IU/kg)	6,681 \pm 1,265	5,280	11,450	26
Vitamin D (IU/kg)	4,450 \pm 1,382	3,000	6,300	4
α -Tocopherol (ppm)	35.24 \pm 8.58	22.5	48.9	12
Thiamine (ppm)	17.27 \pm 2.14	13.0	22.0	26
Riboflavin (ppm)	7.78 \pm 0.899	6.10	9.00	12
Niacin (ppm)	98.73 \pm 23.21	65.0	150.0	12
Pantothenic acid (ppm)	32.94 \pm 8.92	23.0	59.2	12
Pyridoxine (ppm)	9.28 \pm 2.49	5.60	14.0	12
Folic acid (ppm)	2.56 \pm 0.70	1.80	3.70	12
Biotin (ppm)	0.265 \pm 0.046	0.190	0.354	12
Vitamin B ₁₂ (ppb)	41.6 \pm 18.6	10.6	65.0	12
Choline (ppm)	2,955 \pm 382	2,300	3,430	11
Minerals				
Calcium (%)	1.16 \pm 0.05	1.09	1.28	26
Phosphorus (%)	0.92 \pm 0.05	0.760	1.00	26
Potassium (%)	0.886 \pm 0.059	0.772	0.971	10
Chloride (%)	0.531 \pm 0.082	0.380	0.635	10
Sodium (%)	0.316 \pm 0.031	0.258	0.370	12
Magnesium (%)	0.165 \pm 0.010	0.148	0.180	12
Sulfur (%)	0.266 \pm 0.060	0.208	0.420	11
Iron (ppm)	348.0 \pm 83.7	255.0	523.0	12
Manganese (ppm)	93.27 \pm 5.62	81.7	102.0	12
Zinc (ppm)	59.42 \pm 9.73	46.1	81.6	12
Copper (ppm)	11.63 \pm 2.46	8.09	15.4	12
Iodine (ppm)	3.49 \pm 1.14	1.52	5.83	11
Chromium (ppm)	1.57 \pm 0.53	0.60	2.09	12
Cobalt (ppm)	0.81 \pm 0.27	0.49	1.23	8

TABLE M4
Contaminant Levels in NIH-07 Rat and Mouse Ration^a

	Mean \pm Standard Deviation ^b	Range		Number of Samples
Contaminants				
Arsenic (ppm)	0.49 \pm 0.16	0.10	0.70	26
Cadmium (ppm)	0.13 \pm 0.07	0.04	0.20	26
Lead (ppm)	0.36 \pm 0.24	0.10	1.00	26
Mercury (ppm) ^c	<0.02	0.02	0.03	26
Selenium (ppm)	0.32 \pm 0.10	0.05	0.40	26
Aflatoxins (ppb)	<5.0			26
Nitrate nitrogen (ppm) ^d	7.78 \pm 3.83	2.90	17.0	26
Nitrite nitrogen (ppm) ^d	0.18 \pm 0.12	0.10	0.50	26
BHA (ppm) ^e	2.46 \pm 4.04	1.0	20.0	26
BHT (ppm) ^e	1.35 \pm 0.84	1.0	5.0	26
Aerobic plate count (CFU/g)	95,542 \pm 158,814	6,500	710,000	26
Coliform (MPN/g)	3.1 \pm 0.3	3	4	26
<i>Escherichia coli</i> (MPN/g)	<3			26
<i>Salmonella</i> (MPN/g)	Negative			26
Total nitrosoamines (ppb) ^f	7.87 \pm 1.92	4.7	11.4	26
<i>N</i> -Nitrosodimethylamine (ppb) ^f	5.73 \pm 1.31	2.9	8.2	26
<i>N</i> -Nitrosopyrrolidine (ppb) ^f	2.14 \pm 1.26	1.0	6.0	26
Pesticides (ppm)				
α -BHC	<0.01			26
β -BHC	<0.02			26
γ -BHC	<0.01			26
δ -BHC	<0.01			26
Heptachlor	<0.01			26
Aldrin	<0.01			26
Heptachlor epoxide	<0.01			26
DDE	<0.01			26
DDD	<0.01			26
DDT	<0.01			26
HCB	<0.01			26
Mirex	<0.01			26
Methoxychlor	<0.05			26
Dieldrin	<0.01			26
Endrin	<0.01			26
Telodrin	<0.01			26
Chlordane	<0.05			26
Toxaphene	<0.10			26
Estimated PCBs	<0.20			26
Ronnel	<0.01			26
Ethion	<0.02			26
Trithion	<0.05			26
Diazinon	<0.10			26
Methyl parathion	<0.02			26
Ethyl parathion	<0.02			26
Malathion	0.24 \pm 0.23	0.05	0.97	26
Endosulfan I	<0.01			26
Endosulfan II	<0.01			26
Endosulfan sulfate	<0.03			26

^a CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride

^b For values less than the limit of detection, the detection limit is given as the mean.

^c All values except for the lots milled November and December 1991 were less than the detection limit. The detection limit is given as the mean.

^d Sources of contamination: alfalfa, grains, and fish meal

^e Sources of contamination: soy oil and fish meal

^f All values were corrected for percent recovery.

APPENDIX N **SENTINEL ANIMAL PROGRAM**

METHODS	N-2
TABLE N1 Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Studies of Pyridine	N-5

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from randomly selected rats and mice during the 13-week and 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test

Time of Analysis

F344/N RATS

13-Week Study

ELISA

PVM (pneumonia virus of mice)

Study termination

RCV/SDA (rat coronavirus/
sialodacryoadenitis)

Study termination

Sendai

Study termination

Hemagglutination Inhibition

H-1 (Toolan s H-1 virus)

Study termination

KRV (Kilham rat virus)

Study termination

2-Year Study

ELISA

Mycoplasma arthritidis

Study termination

Mycoplasma pulmonis

Study termination

PVM

6, 12, 16, 18, and 19 months, study termination

RCV/SDA

6, 12, 16, 18, and 19 months, study termination

Sendai

6, 12, 16, 18, and 19 months, study termination

Immunofluorescence Assay

Parvovirus

6 months

RCV/SDA

Study termination

Sendai

12 months

Hemagglutination Inhibition

H-1

6, 12, 16, 18, and 19 months, study termination

KRV

6, 12, 16, 18, and 19 months, study termination

WISTAR RATS**13-Week Study**

ELISA

PVM

Study termination

RCV/SDA

Study termination

Sendai

Study termination

Hemagglutination Inhibition

H-1

Study termination

KRV

Study termination

2-Year Study

ELISA

M. arthritidis

6 months, study termination

M. pulmonis

6 months, study termination

PVM

1 week, 3, 5, 6, 12, 14, and 18 months, study termination

RCV/SDA

1 week, 3, 5, 6, 12, 14, and 18 months, study termination

Sendai

1 week, 3, 5, 6, 12, 14, and 18 months, study termination

Immunofluorescence Assay

Parvovirus

3 months, study termination

RCV/SDA

Study termination

Hemagglutination Inhibition

H-1

1 week, 3, 5, 6, 12, 14, and 18 months, study termination

KRV

1 week, 3, 5, 6, 12, 14, and 18 months, study termination

MICE**13-Week Study**

ELISA

Ectromelia virus

Study termination

GDVII (mouse encephalomyelitis virus)

Study termination

LCM (lymphocytic choriomeningitis virus)

Study termination

MHV (mouse hepatitis virus)

Study termination

PVM

Study termination

Reovirus 3

Study termination

Sendai

Study termination

Immunofluorescence Assay

EDIM (epizootic diarrhea of infant mice)

Study termination

Mouse adenoma virus

Study termination

MVM (minute virus of mice)

Study termination

Hemagglutination Inhibition

K (papovavirus)

Study termination

Polyoma virus

Study termination

MICE (continued)**2-Year Study****ELISA**

Ectromelia virus	6, 12, and 18 months, study termination
EDIM	6, 12, and 18 months, study termination
GDVII	6, 12, and 18 months, study termination
LCM	6, 12, and 18 months, study termination
Mouse adenoma virus-FL	6, 12, and 18 months, study termination
MHV	6, 12, and 18 months, study termination
<i>M. arthritidis</i>	Study termination
<i>M. pulmonis</i>	Study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination

Immunofluorescence Assay

GDVII	12 months
MHV	12 months, study termination

Hemagglutination Inhibition

K	6, 12, and 18 months, study termination
MVM	6, 12, and 18 months, study termination
Polyoma virus	6, 12, and 18 months, study termination

Results of serology tests are presented in Table N1.

TABLE N1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Studies of Pyridine

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies		
F344/N Rats		
Study termination	0/10	None positive
Wistar Rats		
Study termination	0/5	None positive
Mice		
Study termination	0/10	None positive
2-Year Studies		
F344/N Rats		
6 Months	1/10	Parvovirus
	1/10	H-1
12 Months	0/10	None positive
16 Months	0/1	None positive
18 Months	0/8	None positive
19 Months	0/1	None positive
Study termination	6/16 ^a	<i>M. arthritidis</i>
Wistar Rats		
1 Week	0/8	None positive
3 Months	1/2	Parvovirus
	1/2	H-1
5 Months	0/1	None positive
6 Months	0/6	None positive
12 Months	0/5	None positive
14 Months	0/1	None positive
18 Months	0/5	None positive
Study termination	0/10	None positive
Mice		
6 Months	0/10	None positive
12 Months	0/8	None positive
18 Months	0/8	None positive
Study termination	0/10	None positive

^a Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only sporadic samples were positive and there were no clinical findings or histopathologic changes of *M. arthritidis* infection in animals with positive titers. Accordingly, *M. arthritidis*-positive titers were considered false positives.

